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14. ABSTRACT- We hypothesize that genetic susceptibility to prostate cancer may be in part due to variations in the core circadian genes that regulate circadian rhythms and that serum sex steroid hormone levels modify the effect that circadian gene variations have on prostate cancer risk. To test this hypothesis, we genotyped and analyzed 256 SNPs in 10 circadian genes in a study of 1,169 prostate cases and 1,365 controls nested within the Prostate Cancer Prevention Trial (PCPT), a randomized placebo-controlled clinical trial to determine if finasteride (an inhibitor of androgen bioactivation) could prevent prostate cancer. Logistic regression analysis using SNPs in an additive model showed that variants in specific circadian genes are associated with prostate cancer risk and that this risk differed between men who took finasteride versus those who took the placebo. The strongest association was seen for a cluster of 9 SNPs in *NPAS2*, which was associated with total prostate cancer risk in the finasteride group but not in the placebo group. The most significant *NPAS2* SNP was rs746924 (finasteride group OR=1.5, $p=9.6x10^{-5}$ versus placebo group OR=0.95, p=0.53). In stratified analysis, the same cluster of *NPAS2* variants and a second cluster of 9 SNPs on *PER3* were associated with low-grade cancers (Gleason sum <7) in the finasteride group but not in the placebo group. Interestingly, risk of high-grade cancers (Gleason sum 7+) in the finasteride group was not related to either the *NPAS2* or *PER3* clusters of SNPs but was associated with a cluster of 7 SNPs in *CRY1.* These findings suggest that it may be possible to use genotyping information to identify men who might benefit from chemoprevention by finasteride and other related drugs. We also found that variations in several circadian genes correlated with serum androgen levels and that these associations may be influenced by finasteride treatment. Most notably, a cluster of 12 SNPs in NPAS2 were associated with percent change in serum testosterone levels between baseline and follow-up. These observations suggest that it is possible that the underlying biology between the association between variations in circadian genes and prostate cancer risk may involve androgens. Future studies are needed to replicate our findings, determine the functional role of the SNPs identified in our study especially as it related to androgen metabolism, and to determine the utility of genotyping information for chemoprevention strategies.

15. SUBJECT TERMS – Prostate cancer; circadian genes; circulating androgens; finasteride

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INTRODUCTION:

Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer death in men in the United States. The only established risk factors for prostate cancer are race, age, and family history (1) but data from recent genome-wide association studies indicate that genetic susceptibility also play a role in the etiology of this disease. We propose that genetic susceptibility to prostate cancer may be in part due to variations in genes from a number of pathways including the core circadian genes that regulate circadian rhythms. This hypothesis is supported by observational studies on sleep duration (2), light at night (3), rotating shift workers (4, 5), and male airline pilots (6-8), which all suggest that circadian rhythm disruptions increase prostate cancer risk. The goal of this project is to test the hypothesis that variants in circadian genes alter the risk of prostate cancer and that serum sex steroid hormone levels modify the effect of circadian polymorphisms on prostate cancer risk. Our study is nested within the Prostate Cancer Prevention Trial (PCPT), a randomized placebo-controlled clinical trial to determine if finasteride (an inhibitor of androgen bioactivation) could prevent prostate cancer. Included in our study are 1,169 cases and 1,365 controls from the PCPT. Questionnaire data, such as age, body mass index, and diabetes status, as well as serum hormone measurements from before and mid-trial are available for these subjects, which makes the PCPT an ideal setting in which to test the hypothesis that genetic susceptibility to prostate cancer may be in part due to variations in the core circadian genes that regulate circadian rhythms and that serum sex steroid hormone levels modify the effect that circadian gene variations have on prostate cancer risk..

BODY:

Our study has three specific aims, all of which utilizes genotyping data that was generated as part of the grant. The following is a summary report of each task in the statement of work:

Task 1. Data management

We have been in constant communications with the PCPT Statistical Center at the Fred Hutchinson Cancer Research Center (Seattle, WA) since the project's inception. Genotyping data for this project has been completed and incorporated into the PCPT central database as are data from serum androgen assays (completed as part of a separate study but used for Aim 2 of this study). With the PCPT Statistical Center, we have completed the quality control analysis of the data (see Task 3 below).

Task 2. Develop and perform genotyping assays on 320 SNPs (including 40 putatively functional and 270 tag SNPs as well as additional SNPs to account for control SNPs and potential SNP assay failures) of circadian genes in 1,169 cases and 1,365 controls.

We completed all genotyping assays for the study. In total, genotyping was performed for 285 single nucleotide polymorphisms (SNPs) on 1,169 cases and 1,365 controls. Thirty five SNPs were not genotyped from the original list because they could not be designed on the chosen genotyping platform or were predicted to have very low (<5%) minor allele frequencies in the reference population (HapMap Caucasian population, CEU). Study subjects who were not included in the genotyping did not have sufficiently DNA for genotyping; for these subjects, alternative strategies, including use of serum, were considered but the assays were cost-prohibitive due to additional costs involved for sample processing. A comparison of select characteristics (e.g., age, body mass index, etc) between the genotyped versus not genotyped subjects showed no significant differences

between the 2 subsets of subjects and thus we do not believe bias was introduced due to the reduced sample size.

Task 3. Monitor quality of genotyping results on an ongoing basis

Quality of the genotyping was assessed for SNPs as well as for samples:

SNPs. We assessed SNP genotyping quality by calculating completion rates (i.e., percentage of subjects for whom genotypes were called), concordance rates (for any SNP, the percentage of replicate samples that had the identical genotype called), and Hardy-Weinberg Equilibrium (HWE) p-values. Based on data from all subjects combined (N=2,534), completion rates ranged from 49% to 100%. Specifically, of the 285 SNPs that were typed, completion rates were >75% for 265 (93%) SNPs and >95% for 209 (73%) SNPs. No significant differences in completion rates were seen between cases and controls. For concordance rates, we assessed data from 228 subjects (all control subjects) for whom duplicate DNA were typed for the 285 SNPs. Concordance rate between the 228 sets of duplicate samples ranged from 50.4% to 99.6%; Of the 285 SNPs, concordance rates were >75% for 271 SNPs (96%) and >95% for 197 SNPs (69%). We also assessed Hardy-Weinberg Equlibrium for all SNPs in the control population. HWE p-values ranged from <0.0001 to 1; of the 285 SNPs typed, 265 (82%) had HWE p-value >0.001. For inclusion in subsequent analysis, we included SNPs for which completion rates were >75%, concordance rates were >75%, and HWE p-values were >0.001. In total, 256 SNPs met these criteria.

Subjects. We assessed quality of the samples for each subject by the completion rates as defined as the percentage of SNPs that were successfully genotyped on each sample. Using data from the 256 SNPs that passed quality control described above, 2,126 subjects (83.8%) had data for over 250 SNPs (97.7% completion rate) and all 2,534 subjects had data for over 192 SNPs (75% completion rate). For inclusion in subsequent analysis, we included subjects for which completion rates were >75%. In total, 1,169 prostate cases and 1,365 controls were included in subsequent analysis (Table 1).

Task 4. Gather, ship, process, and archive biospecimens

The DNAs were shipped to and genotyped at the core genotyping facility at the University of Texas Health Science Center in San Antonio. This task was the most time consuming as the PCPT biorepository at the NCI had a backlog of requests for sample preparation for genotyping. In addition, the PCPT cohort changed genotyping laboratories for all PCPT genetic studies in 2010.

Task 5. Prepare hormone data from PCPT

As part of a separately funded study, we worked with the PCPT Statistical Center on analyzing data related to serum androgen levels as part of the PCPT Program Project. Dr. Ann Hsing, the PI of the current award, led the analysis and is the senior author of the recently published main manuscript describing the results (9). We use the androgen data from this previous study, including how the variables are categorized, in Aim 2 of the current study.

Tasks 6. Perform statistical analysis

Statistical analysis has been completed for main effects of SNPs in circadian genes on prostate cancer risk (Aim 1; Tables 2-3 & Figures 1-3) and serum androgen levels (Aim 3; Tables 4-5 &

Figures 4-6). We are currently finalizing the gene- and circadian pathway-based analyses. This part of the analysis was delayed due to the updating of the statistical software used for the analysis (10), which was released in August 2012 (AdaJoint; http://dceg.cancer.gov/bb/tools/AdaJoint). We anticipate this analysis will be completed by January 2013.

For Aim 2, we are currently analyzing the joint effects between SNPs and serum androgens on prostate cancer risk. This analysis requires a higher level of statistical analysis than Aims 1 and 3 and thus takes more time to accomplish. We anticipate this analysis to be completed by April 2013.

Task 7. Prepare scientific presentations & manuscripts

Preliminary data on a subset of the genotyping data was presented at the DoD PCRP IMPaCT Meeting in Orlando, FL in March 2011.

We are currently finalizing the gene- and circadian pathway-based analysis for Aims 1 and 3. Once the gene- and pathway-based analyses are complete, we will draft the manuscripts (separately for Aims 1 and 3) and anticipate submission of the manuscript to a peer-reviewed journal (e.g., Cancer Research, Cancer Prevention Research, etc) within 6 months time. Similarly, we anticipate completion of statistical analysis for Aim 2 by April 2013 with a subsequent manuscript to be drafted and submitted to a peer-reviewed journal within 6 month from end of analysis.

KEY RESEARCH ACCOMPLISHMENTS:

- Our study showed risks for prostate cancer related to variations in circadian genes are different between the finasteride group and the placebo group of the PCPT (Table 2). This suggests that finasteride modifies the effect that SNPs in circadian genes have on prostate cancer risk.
    - A cluster of 9 SNPs in *NPAS2* was associated with total prostate cancer risk in the finasteride group but not in the placebo group (Tables 2-3 & Figure 1). The most significant *NPAS2* SNP was rs746924 (finasteride group: OR=1.5, $p=9.6x10^{-5}$ versus placebo group: OR=0.95, p=0.53); this SNP reached Bonferroni-corrected p-value threshold of $1.95x10^{-4}$.
    - The same cluster of *NPAS2* SNPs and a cluster of 9 SNPs in *PER3* were associated with risk for low-grade prostate cancer in the finasteride treated group and not in the placebo group (Tables 2-3 & Figure 2).
    - For high-grade prostate cancer, neither the *NPAS2* nor the *PER3* SNP clusters were associated with risk in the finasteride group but a cluster of 7 SNPs in *CRY1* was associated with risk in the finasteride group but not in the placebo group (Tables 2-3 & Figure 3).

- Our study also showed correlation between some SNPs in specific circadian genes and serum androgen and SHBG levels (Table 4). These correlations also seem to be influenced by finasteride treatment (Table 4).
    - Most notably, 12 SNPs in *NPAS2* were associated with percent change in serum testosterone levels between baseline and follow-up (Tables 4-5 & Figure 4).
    - No obvious cluster of SNPs in any circadian gene was associated with baseline, follow-up, or percent change in 3α diol G (Table 4 & Figure 5). Several individual SNPs in *CSNK1E*, *NPAS2*, and *PER3* were correlated with 3α diol G at baseline and follow-up at p<0.01.

- Several variants in *NPAS2* were associated with serum SHBG during finasteride treatment but not with change in SHBG levels between baseline and follow-up (Tables 4-5 & Figure 6)

REPORTABLE OUTCOMES: Provide a list of reportable outcomes that have resulted from this research to include:

- Presentations
  - DoD PCRP IMPaCT Meeting in Orlando, FL in March 2011.
- Manuscripts
  - At least two manuscripts to be submitted within 6-12 months of this report
- Informatics such as databases
  - Data from 285 SNPs have been added to the PCPT database at the statistical center.
- Funding applied for based on work supported by this award
  - R03 Circadian Genes and Aggressive Prostate Cancer in Caucasians and African Americans (PI: Ann Hsing, submitted July 2012)
- Employment or research opportunities applied for and/or received based on experience/training supported by this award
  - Co-PI (Lisa Chu) is now a Senior Staff Scientist at the Cancer Prevention Institute of California

CONCLUSION:

The goal of this project was to test the novel hypothesis that variants in circadian genes alter the risk of prostate cancer and that serum sex steroid hormone levels modify the effect of circadian polymorphisms on prostate cancer risk. Through our preliminary analysis of the data for prostate cancer risk (total, low- and high-grade cancers), we show that certain variants in specific circadian genes influences prostate cancer risk. We also show that the effects of the SNPs on prostate cancer risk are modifiable by treatment with finasteride. We see similar effects when restricting our analysis to low- and high-grade prostate cancers. These results show that it may be possible to develop methods to use genotyping information to select men who might benefit from chemoprevention. We also showed that some variations in circadian genes correlate with serum androgen levels and that this correlation may be influenced by finasteride treatment. These observations suggest that it is possible that the underlying biology between the association between variations in circadian genes and prostate cancer risk may involve androgens. Future studies are needed to replicate our findings, determine the functional role of the SNPs identified in our study especially as it related to androgen metabolism, and to determine the utility of genotyping information for chemoprevention trials.

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APPENDICES:

NONE

SUPPORTING DATA:

Tables

Figures

Table 1. Select Characteristics of Study Subjects

						Placebo Group								Finasteride Group							
	Total					White				Minority				White				Minority			
	Controls		Cases			Controls		Cases		Controls		Cases		Controls		Cases		Controls		Cases	
Characteristic (categorical)	**n**	**%**	**n**	**%**	**p-value**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Number of Participants	1365		1169			667		642		118		43		422		450		158		34	
Body Mass Index (BMI; Baseline)					0.09																
Normal (BMI <25)	328	24.3%	324	28.0%		157	23.9%	192	30.2%	24	20.3%	7	16.3%	106	25.2%	117	26.2%	41	26.3%	8	23.5%
Overweight (BMI 25 to <30)	718	53.2%	598	51.6%		357	54.4%	331	52.1%	63	53.4%	22	51.2%	234	55.7%	227	50.8%	64	41.0%	18	52.9%
Obese (BMI >=30)	304	22.5%	237	20.4%		142	21.6%	112	17.6%	31	26.3%	14	32.6%	80	19.0%	103	23.0%	51	32.7%	8	23.5%
Alcohol Consumption					0.25																
Non-drinker	320	23.4%	243	20.8%		150	22.5%	132	20.6%	33	28.0%	12	27.9%	99	23.5%	90	20.0%	38	24.1%	9	26.5%
>0 to <30 g/day Alcohol	928	68.0%	816	69.8%		458	68.7%	455	70.9%	75	63.6%	29	67.4%	281	66.6%	308	68.4%	114	72.2%	24	70.6%
>=30 g/day Alcohol	117	8.6%	110	9.4%		59	8.8%	55	8.6%	10	8.5%	2	4.7%	42	10.0%	52	11.6%	6	3.8%	1	2.9%
Smoking Status					0.21																
Never Smoker	454	33.3%	414	35.4%		230	34.5%	229	35.7%	35	29.7%	15	34.9%	149	35.3%	159	35.3%	40	25.3%	11	32.4%
Current Smoke	103	7.5%	70	6.0%		45	6.7%	34	5.3%	17	14.4%	7	16.3%	25	5.9%	26	5.8%	16	10.1%	3	8.8%
Former Smoker	808	59.2%	685	58.6%		392	58.8%	379	59.0%	66	55.9%	21	48.8%	248	58.8%	265	58.9%	102	64.6%	20	58.8%
Has Family History of Prostate Cancer	290	21.2%	245	21.0%	0.86	142	21.3%	135	21.0%	19	16.1%	7	16.3%	106	25.1%	101	22.4%	23	14.6%	2	5.9%
Has Diabetes	109	8.0%	51	4.4%	<0.001	44	6.6%	21	3.3%	16	13.7%	3	7.0%	17	4.0%	21	4.7%	32	20.3%	6	17.6%
Race					<0.0001																
White (Non-Hispanic)	1089	79.8%	1092	93.4%		667	100.0%	642	100.0%					422	100.0%	450	100.0%				
Black	130	9.5%	47	4.0%						49	41.5%	27	62.8%					81	51.3%	20	58.8%
Other	146	10.7%	30	2.6%						69	58.5%	16	37.2%					77	48.7%	14	41.2%
Gleason Sum																					
2-6			829	73.4%				499	80.3%			28	68.2%			283	65.2%			19	55.9%
7-10			301	26.6%				122	19.6%			13	31.8%			151	34.8%			15	44.1%
T-stage																					
T1 a/b/c			903	79.3%				506	80.8%			31	75.6%			341	78.0%			25	73.5%
T2 a/b/c			221	19.4%				113	18.1%			9	22.0%			90	20.6%			9	26.5%
T 3/4			14	1.2%				7	1.1%			1	2.4%			6	1.4%				
N-stage																					
N X/0			1110	99.5%				607	99.3%			41	100.0%			428	99.5%			34	100.0%
N 1/2			6	0.5%				4	0.7%							2	0.5%				
M-stage																					
M X/0			1113	99.7%				609	99.7%			41	100.0%			429	99.8%			34	100.0%
M1			3	0.3%				2	0.3%							1	0.2%				
Characteristics (continuous)	**Mean**	**SD**	**Mean**	**SD**		**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (Baseline)	63.61	0.06	63.44	0.06	0.46	63.75	5.66	63.48	5.59	62.14	4.95	61.51	4.98	64.33	5.76	63.58	5.57	62.16	5.01	63.26	6.13
BMI (Baseline)	27.71	4.02	27.41	4.04	0.06	27.63	3.96	27.14	4.02	28.03	4.07	29.38	5.50	27.61	3.92	27.55	3.82	28.10	4.47	28.15	4.35
Alcohol Consumption, g/day	9.15	14.03	10.02	14.71	0.12	9.27	13.81	9.48	13.39	9.00	16.64	6.65	10.14	9.71	14.49	11.50	16.95	7.20	11.33	5.12	7.72
Pack-Years of Cigarettes Smoked	15.54	16.90	13.55	15.79	<0.01	16.03	17.55	13.18	15.41	14.90	15.86	10.99	14.45	15.72	16.96	14.41	16.44	13.47	14.48	12.53	15.70

Table 2. Summary of variants in circadian genes and their associations with prostate cancer

		# SNPs associated with Total Prostate Cancer Risk				# SNPs associated with Low-Grade Prostate Cancer Risk				# SNPs associated with High-Grade Prostate Cancer Risk			
	# SNPs	Placebo Group		Finasteride Group		Placebo Group		Finasteride Group		Placebo Group		Finasteride Group	
Gene	Genotyped	p<0.01	p<0.05	p<0.01	p<0.05	p<0.01	p<0.05	p<0.01	p<0.05	p<0.01	p<0.05	p<0.01	p<0.05
ARNTL	28	0	0	1	4	0	2	0	3	0	0	1	1
CLOCK	14	0	0	0	1	0	0	0	0	0	0	0	1
CRY1	22	1	4	0	1	1	5	0	0	0	0	3	7
CRY2	16	0	0	0	0	0	0	0	0	1	2	0	0
CSNK1E	23	0	2	0	1	0	3	0	0	1	2	0	0
NPAS2	79	1	3	7	9	0	1	6	10	1	4	0	1
PER1	17	0	1	0	1	0	0	0	0	0	1	0	0
PER2	24	0	1	0	0	0	0	0	0	1	5	0	0
PER3	30	0	0	0	3	0	1	2	9	1	6	0	1
TIMELESS	2	0	0	0	0	0	0	0	0	0	0	0	0
Total	*255*	*2*	*11*	*8*	*20*	*1*	*12*	*8*	*22*	*5*	*20*	*4*	*11*

Table 3. Odds ratios (OR) and 95% confidence intervals (CI) for total, low-, and high-grade prostate cancer in relation to SNPs in circadian genes with P-value <0.05 in the PCPT nested case-control study

p<0.01

p<0.05

				Total Prostate Cancer Risk									
				Placebo Group					Finasteride Group				
				MAF					MAF				
Gene	SNP	Chr	Location	Controls	Cases	OR	95% CI	p-value	Controls	Cases	OR	95% CI	p-value
ARNTL	rs7924734	11	13350747	0.26	0.26	0.98	0.81 - 1.17	0.7854	0.26	0.28	1.06	0.86 - 1.3	0.5809
	rs6486121	11	13355770	0.37	0.37	1.02	0.86 - 1.2	0.8337	0.34	0.40	1.28	1.04 - 1.56	0.0170
	rs7947951	11	13356030	0.31	0.33	1.08	0.91 - 1.28	0.3846	0.31	0.36	1.24	1.01 - 1.52	0.0388
	rs1026071	11	13364712	0.28	0.30	1.1	0.93 - 1.31	0.2536	0.29	0.33	1.19	0.97 - 1.47	0.1000
	rs969486	11	13403135	0.28	0.29	1.05	0.88 - 1.26	0.5595	0.31	0.26	0.81	0.66 - 0.99	0.0406
	rs11022825	11	13456195	0.19	0.19	1.01	0.83 - 1.24	0.9142	0.15	0.20	1.4	1.09 - 1.8	0.007990
CLOCK	rs6850524	4	56381997	0.42	0.42	1.01	0.86 - 1.19	0.8927	0.43	0.41	0.92	0.75 - 1.11	0.3704
	rs2087319	4	56461365	0.25	0.26	1.04	0.87 - 1.24	0.6450	0.22	0.26	1.26	1.01 - 1.58	0.0415
CRY1	rs7974499	12	107341385	0.46	0.49	1.14	0.97 - 1.33	0.1096	0.45	0.47	1.08	0.9 - 1.31	0.4077
	rs4640029	12	107378724	0.42	0.47	1.22	1.04 - 1.44	0.0141	0.43	0.44	1.02	0.85 - 1.23	0.8220
	rs714359	12	107378845	0.22	0.20	0.9	0.75 - 1.09	0.3026	0.21	0.23	1.1	0.87 - 1.38	0.4304
	rs2287161	12	107381140	0.50	0.45	0.8	0.67 - 0.96	0.0134					
	rs1056560	12	107385610	0.43	0.45	1.08	0.93 - 1.27	0.3166	0.40	0.43	1.16	0.95 - 1.42	0.1377
	rs8192440	12	107395106	0.36	0.39	1.13	0.96 - 1.33	0.1421	0.34	0.38	1.19	0.97 - 1.46	0.0916
	rs10778528	12	107473962	0.40	0.43	1.11	0.95 - 1.3	0.2059	0.37	0.41	1.19	0.97 - 1.45	0.0912
	rs10778533	12	107499077	0.18	0.16	0.91	0.74 - 1.11	0.3406	0.17	0.19	1.16	0.9 - 1.49	0.2591
	rs1921141	12	107514641	0.39	0.37	0.9	0.77 - 1.06	0.2221	0.43	0.38	0.8	0.66 - 0.98	0.0289
	rs2204830	12	107527163	0.11	0.09	0.8	0.62 - 1.03	0.0882	0.08	0.08	0.88	0.62 - 1.26	0.5010
	rs11113198	12	107532255	0.50	0.46	0.85	0.73 - 1	0.0431	0.50	0.47	0.88	0.73 - 1.06	0.1912
	rs4432103	12	107535603	0.32	0.37	1.25	1.06 - 1.48	0.0090	0.31	0.36	1.21	0.99 - 1.48	0.0590
CRY2	rs1139266	11	45832935	0.21	0.23	1.14	0.92 - 1.41	0.2392					
	rs7951225	11	45875392	0.18	0.19	1.07	0.87 - 1.3	0.5261	0.19	0.21	1.12	0.88 - 1.43	0.3493
CSNK1E	rs9610926	22	38653575	0.30	0.28	0.89	0.75 - 1.06	0.1799	0.32	0.29	0.91	0.75 - 1.11	0.3607
	rs135715	22	38660871	0.39	0.39	0.98	0.84 - 1.16	0.8506	0.41	0.36	0.82	0.68 - 0.99	0.0404
	rs9622771	22	38675738	0.17	0.16	0.91	0.74 - 1.12	0.3684	0.18	0.16	0.85	0.66 - 1.08	0.1798
	rs1997644	22	38715222	0.44	0.48	1.18	1.01 - 1.38	0.0410	0.47	0.47	0.95	0.78 - 1.15	0.5925
	rs13054361	22	38732824	0.08	0.07	0.92	0.69 - 1.23	0.5751	0.09	0.07	0.75	0.52 - 1.07	0.1151
	rs763220	22	38744727	0.08	0.08	1.04	0.76 - 1.42	0.8082	0.06	0.07	1.17	0.78 - 1.76	0.4407
	rs5757058	22	38749925	0.51	0.49	0.91	0.77 - 1.08	0.2685	0.51	0.50	0.96	0.79 - 1.17	0.7033
NPAS2	rs10194413	2	101518910	0.08	0.10	1.24	0.93 - 1.64	0.1396	0.09	0.10	1.1	0.79 - 1.53	0.5606
	rs356652	2	101540415	0.08	0.09	1.18	0.89 - 1.55	0.2542	0.08	0.11	1.41	1.02 - 1.95	0.0362
	rs12712085	2	101565151	0.45	0.39	0.79	0.67 - 0.93	0.0040	0.41	0.46	1.21	1 - 1.47	0.0518
	rs3820787	2	101566234	0.37	0.33	0.82	0.7 - 0.97	0.0212	0.36	0.37	1.04	0.85 - 1.28	0.6957
	rs876060	2	101576964	0.20	0.22	1.1	0.9 - 1.35	0.3333	0.20	0.23	1.24	0.98 - 1.58	0.0766
	rs6738097	2	101578542	0.14	0.14	1.04	0.83 - 1.3	0.7195	0.13	0.16	1.25	0.96 - 1.63	0.1018
	rs4851392	2	101581976	0.30	0.26	0.82	0.69 - 0.98	0.0275	0.28	0.30	1.11	0.89 - 1.37	0.3532
	rs6719437	2	101599071	0.34	0.34	1.06	0.89 - 1.25	0.5283	0.35	0.30	0.79	0.65 - 0.97	0.0256
	rs11123857	2	101603812	0.28	0.29	1.1	0.93 - 1.3	0.2756	0.28	0.26	0.92	0.74 - 1.14	0.4283
	rs1053096	2	101612615	0.34	0.33	0.95	0.81 - 1.13	0.5763	0.29	0.36	1.38	1.12 - 1.7	0.0020
	rs935401	2	101613409	0.44	0.45	1.06	0.91 - 1.24	0.4344	0.49	0.41	0.74	0.61 - 0.9	0.0021
	rs10934	2	101622728	0.29	0.30	1.04	0.88 - 1.24	0.6154	0.35	0.27	0.68	0.55 - 0.84	0.0002
	rs11695176	2	101623667	0.17	0.16	0.92	0.75 - 1.13	0.4281	0.19	0.14	0.67	0.52 - 0.88	0.0030
	rs746924	2	101624471	0.34	0.33	0.95	0.81 - 1.12	0.5304	0.29	0.38	1.49	1.22 - 1.83	0.0001
	rs4850956	2	101628324	0.49	0.48	0.98	0.84 - 1.14	0.7619	0.43	0.52	1.43	1.18 - 1.73	0.0002
	rs12472882	2	101646359	0.29	0.30	1.02	0.86 - 1.21	0.8214	0.35	0.27	0.68	0.55 - 0.84	0.0003
PER1	rs3809881	17	7999957	0.41	0.43	1.09	0.93 - 1.28	0.3067	0.42	0.37	0.81	0.66 - 0.99	0.0416
	rs8067165	17	8031936	0.40	0.36	0.85	0.73 - 0.99	0.0407	0.39	0.41	1.08	0.89 - 1.32	0.4093
	rs3027267	17	8090895	0.08	0.08	0.91	0.67 - 1.23	0.5317	0.09	0.08	0.98	0.68 - 1.4	0.9121
PER2	hCV27848035	2	239153948	0.16	0.13	0.82	0.66 - 1.03	0.0812	0.15	0.15	1.01	0.77 - 1.32	0.9316
	rs11894535	2	239177073	0.23	0.20	0.86	0.71 - 1.05	0.1436	0.23	0.24	1.04	0.82 - 1.32	0.7327
	rs2304674	2	239181904	0.27	0.26	0.93	0.78 - 1.11	0.4501	0.28	0.28	1.01	0.82 - 1.25	0.9188
	rs2304673	2	239185922	0.15	0.13	0.8	0.64 - 1	0.0491	0.15	0.15	1.05	0.8 - 1.37	0.7206
PER3	rs1417986	1	7797734	0.37	0.38	1.03	0.87 - 1.22	0.7198	0.38	0.38	1.02	0.84 - 1.24	0.8396
	rs2066293	1	7810543	0.27	0.29	1.12	0.94 - 1.34	0.2040	0.30	0.30	1.01	0.82 - 1.25	0.9053
	rs707455	1	7825311	0.42	0.43	1.07	0.91 - 1.25	0.4347	0.42	0.44	1.04	0.86 - 1.26	0.6536
	rs1773157	1	7834858	0.16	0.16	0.95	0.77 - 1.17	0.6286	0.17	0.14	0.83	0.64 - 1.08	0.1692
	rs697673	1	7837842	0.23	0.22	0.91	0.75 - 1.1	0.3322	0.25	0.21	0.79	0.63 - 1	0.0482
	rs1048785	1	7841330	0.13	0.12	0.89	0.7 - 1.12	0.3258	0.11	0.13	1.2	0.89 - 1.62	0.2222
	rs697686	1	7850218	0.35	0.36	1.07	0.91 - 1.26	0.4426	0.34	0.37	1.12	0.92 - 1.36	0.2729
	rs875994	1	7852919	0.17	0.17	0.97	0.79 - 1.2	0.7924	0.15	0.17	1.17	0.91 - 1.51	0.2254
	rs12141033	1	7878547	0.38	0.39	1.09	0.93 - 1.28	0.3050	0.37	0.39	1.05	0.86 - 1.28	0.61775
	rs10462020	1	7880683	0.19	0.18	0.94	0.77 - 1.16	0.5742	0.17	0.19	1.17	0.91 - 1.49	0.2133
	rs17374439	1	7888438	0.19	0.18	0.95	0.78 - 1.17	0.6559	0.17	0.19	1.14	0.89 - 1.45	0.2890
	rs12741937	1	7897622	0.16	0.16	0.98	0.78 - 1.21	0.8269	0.13	0.16	1.25	0.95 - 1.65	0.10476
	rs12731471	1	7904699	0.11	0.11	1.02	0.78 - 1.33	0.8845	0.08	0.12	1.46	1.04 - 2.05	0.0262
	rs707476	1	7918106	0.34	0.33	0.96	0.81 - 1.14	0.6389	0.31	0.32	1.07	0.87 - 1.31	0.51389
	rs531485	1	7921952	0.24	0.22	0.89	0.73 - 1.07	0.2138	0.20	0.22	1.12	0.88 - 1.44	0.3544
	rs12566535	1	7924094	0.10	0.10	0.97	0.75 - 1.25	0.8039	0.13	0.10	0.71	0.52 - 0.97	0.0292

		Low Grade Prostate Cancer Risk									
		Placebo Group					Finasteride Group				
		MAF					MAF				
Gene	SNP	Controls	Cases	*OR*	*95% CI*	*p-value*	Controls	Cases	*OR*	*95% CI*	*p-value*
ARNTL	rs7924734	0.26	0.25	0.96	0.78 - 1.17	0.6619	0.25	0.31	1.33	1.06 - 1.68	0.0157
	rs6486121	0.36	0.39	1.14	0.95 - 1.36	0.1565	0.36	0.42	1.30	1.04 - 1.63	0.0234
	rs7947951	0.30	0.35	1.22	1.01 - 1.47	0.0353	0.31	0.38	1.30	1.03 - 1.63	0.0262
	rs1026071	0.28	0.32	1.21	1 - 1.46	0.0460	0.31	0.36	1.21	0.96 - 1.53	0.1074
	rs969486	0.29	0.28	0.98	0.81 - 1.19	0.8203	0.29	0.25	0.85	0.66 - 1.08	0.1765
	rs11022825	0.18	0.19	1.03	0.82 - 1.29	0.8229	0.17	0.20	1.21	0.92 - 1.61	0.1799
CLOCK	rs6850524	0.42	0.42	1.02	0.85 - 1.22	0.8398	0.42	0.40	0.89	0.71 - 1.12	0.3269
	rs2087319	0.24	0.26	1.09	0.9 - 1.32	0.3784	0.23	0.27	1.24	0.96 - 1.6	0.0995
CRY1	rs7974499	0.46	0.50	1.15	0.97 - 1.37	0.1044	0.46	0.46	0.97	0.78 - 1.21	0.8086
	rs4640029	0.42	0.47	1.21	1.01 - 1.45	0.0342	0.44	0.42	0.93	0.74 - 1.16	0.5247
	rs714359	0.22	0.19	0.79	0.64 - 0.98	0.0341	0.22	0.24	1.14	0.87 - 1.48	0.3454
	rs2287161	0.49	0.44	0.80	0.66 - 0.97	0.0243					
	rs1056560	0.43	0.44	1.04	0.87 - 1.24	0.6547	0.42	0.43	1.04	0.82 - 1.31	0.7437
	rs8192440	0.36	0.38	1.08	0.9 - 1.29	0.3910	0.36	0.37	0.99	0.79 - 1.26	0.9599
	rs10778528	0.40	0.42	1.08	0.91 - 1.29	0.3800	0.39	0.41	1.04	0.82 - 1.31	0.7558
	rs10778533	0.18	0.16	0.90	0.71 - 1.13	0.3606	0.18	0.18	0.97	0.73 - 1.3	0.8491
	rs1921141	0.39	0.37	0.93	0.77 - 1.11	0.4228	0.41	0.37	0.86	0.68 - 1.08	0.1923
	rs2204830	0.12	0.08	0.69	0.52 - 0.92	0.0093	0.09	0.08	0.97	0.64 - 1.45	0.8740
	rs11113198	0.50	0.46	0.86	0.73 - 1.02	0.0887	0.49	0.50	1.03	0.83 - 1.28	0.7877
	rs4432103	0.32	0.37	1.23	1.02 - 1.48	0.029045	0.33	0.33	1.00	0.79 - 1.26	0.9947
CRY2	rs1139266	0.23	0.22	0.91	0.72 - 1.16	0.4555					
	rs7951225	0.19	0.18	0.92	0.74 - 1.15	0.4524	0.19	0.23	1.30	0.99 - 1.71	0.0613
CSNK1E	rs9610926	0.31	0.27	0.82	0.67 - 0.99	0.0399	0.31	0.30	0.96	0.76 - 1.21	0.7366
	rs135715	0.40	0.38	0.88	0.74 - 1.06	0.1722	0.41	0.36	0.82	0.66 - 1.03	0.0854
	rs9622771	0.18	0.14	0.77	0.6 - 0.98	0.0318	0.18	0.15	0.78	0.58 - 1.05	0.1003
	rs1997644	0.45	0.49	1.17	0.98 - 1.39	0.0733	0.48	0.46	0.89	0.71 - 1.11	0.3074
	rs13054361	0.08	0.09	1.13	0.83 - 1.53	0.4551	0.08	0.06	0.76	0.49 - 1.17	0.2049
	rs763220	0.09	0.07	0.72	0.5 - 1.03	0.0670	0.07	0.06	0.89	0.55 - 1.44	0.6401
	rs5757058	0.51	0.47	0.83	0.69 - 1	0.0485	0.51	0.48	0.86	0.68 - 1.09	0.2090
NPAS2	rs10194413	0.07	0.10	1.44	1.05 - 1.96	0.0233	0.10	0.10	1.08	0.74 - 1.57	0.6824
	rs356652	0.08	0.10	1.23	0.91 - 1.66	0.1877	0.09	0.11	1.27	0.89 - 1.81	0.1924
	rs12712085	0.44	0.40	0.84	0.71 - 1	0.05565	0.42	0.47	1.22	0.98 - 1.53	0.0737
	rs3820787	0.36	0.35	0.92	0.77 - 1.11	0.3983	0.36	0.37	1.05	0.82 - 1.33	0.7170
	rs876060	0.21	0.22	1.02	0.82 - 1.27	0.8375	0.20	0.26	1.42	1.09 - 1.85	0.0101
	rs6738097	0.15	0.14	0.95	0.74 - 1.21	0.6514	0.14	0.19	1.50	1.11 - 2.01	0.0079
	rs4851392	0.29	0.27	0.92	0.76 - 1.12	0.4203	0.28	0.30	1.06	0.83 - 1.36	0.6228
	rs6719437	0.33	0.35	1.07	0.89 - 1.28	0.4902	0.34	0.28	0.74	0.58 - 0.94	0.0130
	rs11123857	0.28	0.28	1.03	0.86 - 1.25	0.7236	0.27	0.27	0.97	0.76 - 1.25	0.8166
	rs1053096	0.34	0.33	0.99	0.82 - 1.19	0.8992	0.31	0.38	1.36	1.07 - 1.72	0.0110
	rs935401	0.44	0.45	1.05	0.88 - 1.24	0.6011	0.46	0.41	0.78	0.62 - 0.97	0.0283
	rs10934	0.29	0.30	1.03	0.86 - 1.24	0.7475	0.33	0.26	0.70	0.55 - 0.9	0.0052
	rs11695176	0.17	0.16	0.96	0.76 - 1.2	0.7030	0.18	0.13	0.65	0.47 - 0.9	0.0076
	rs746924	0.34	0.33	0.98	0.82 - 1.17	0.8075	0.32	0.39	1.42	1.13 - 1.78	0.0029
	rs4850956	0.48	0.49	1.01	0.85 - 1.2	0.8760	0.45	0.53	1.38	1.11 - 1.73	0.0040
	rs12472882	0.29	0.29	1.00	0.83 - 1.2	0.9826	0.33	0.26	0.71	0.55 - 0.91	0.0068
PER1	rs3809881	0.41	0.43	1.09	0.92 - 1.31	0.3225	0.41	0.37	0.88	0.69 - 1.11	0.2787
	rs8067165	0.40	0.36	0.86	0.73 - 1.03	0.1000	0.40	0.42	1.14	0.92 - 1.43	0.2389
	rs3027267	0.07	0.08	1.06	0.76 - 1.48	0.7291	0.09	0.07	0.78	0.5 - 1.22	0.2683
PER2	hCV27848035	0.15	0.14	0.93	0.73 - 1.18	0.5351	0.15	0.16	1.12	0.82 - 1.54	0.4834
	rs11894535	0.21	0.22	1.05	0.84 - 1.3	0.6832	0.24	0.24	1.01	0.77 - 1.33	0.9216
	rs2304674	0.26	0.28	1.07	0.88 - 1.29	0.5005	0.28	0.27	0.97	0.75 - 1.24	0.7839
	rs2304673	0.14	0.13	0.92	0.72 - 1.18	0.5176	0.15	0.15	1.09	0.79 - 1.49	0.6040
PER3	rs1417986	0.37	0.38	1.02	0.85 - 1.22	0.8136	0.40	0.34	0.78	0.62 - 0.98	0.0306
	rs2066293	0.27	0.29	1.13	0.93 - 1.37	0.2126	0.30	0.28	0.88	0.69 - 1.12	0.3029
	rs707455	0.41	0.44	1.13	0.95 - 1.35	0.1577	0.43	0.42	0.95	0.76 - 1.18	0.6431
	rs1773157	0.17	0.16	0.95	0.75 - 1.19	0.6323	0.18	0.12	0.68	0.49 - 0.94	0.0163
	rs697673	0.23	0.22	0.89	0.72 - 1.1	0.2996	0.25	0.18	0.66	0.5 - 0.88	0.0036
	rs1048785	0.13	0.12	0.87	0.67 - 1.13	0.3053	0.11	0.15	1.43	1.04 - 1.98	0.0310
	rs697686	0.34	0.37	1.17	0.98 - 1.4	0.0910	0.35	0.36	1.05	0.83 - 1.31	0.6910
	rs875994	0.17	0.17	0.95	0.76 - 1.19	0.6635	0.15	0.20	1.39	1.04 - 1.85	0.0245
	rs12141033	0.37	0.40	1.18	0.99 - 1.41	0.0602	0.39	0.38	0.95	0.76 - 1.19	0.6520
	rs10462020	0.19	0.18	0.91	0.73 - 1.14	0.4168	0.17	0.22	1.40	1.07 - 1.84	0.0161
	rs17374439	0.19	0.18	0.92	0.74 - 1.16	0.4874	0.17	0.22	1.37	1.05 - 1.8	0.0232
	rs12741937	0.16	0.16	1.06	0.84 - 1.35	0.6238	0.14	0.17	1.24	0.91 - 1.68	0.1739
	rs12731471	0.11	0.11	1.10	0.83 - 1.48	0.5003	0.09	0.13	1.50	1.04 - 2.16	0.0309
	rs707476	0.35	0.32	0.87	0.72 - 1.04	0.1289	0.32	0.33	1.07	0.85 - 1.36	0.5512
	rs531485	0.25	0.21	0.80	0.65 - 0.99	0.0374	0.20	0.24	1.32	1 - 1.75	0.0542
	rs12566535	0.09	0.10	1.10	0.82 - 1.47	0.5330	0.13	0.08	0.59	0.4 - 0.87	0.0060

		High Grade Prostate Cancer Risk									
		Placebo Group					Finasteride Group				
		MAF					MAF				
Gene	SNP	Controls	Cases	*OR*	*95% CI*	*p-value*	Controls	Cases	*OR*	*95% CI*	*p-value*
ARNTL	rs7924734	0.25	0.25	0.97	0.67 - 1.41	0.8763	0.26	0.22	0.82	0.57 - 1.17	0.2679
	rs6486121	0.37	0.33	0.84	0.59 - 1.19	0.3205	0.37	0.35	0.97	0.7 - 1.35	0.8714
	rs7947951	0.32	0.27	0.78	0.54 - 1.13	0.1800	0.33	0.28	0.85	0.6 - 1.2	0.3542
	rs1026071	0.29	0.24	0.79	0.54 - 1.14	0.1997	0.31	0.29	0.98	0.69 - 1.39	0.9143
	rs969486	0.28	0.31	1.18	0.82 - 1.69	0.3721	0.28	0.27	0.93	0.66 - 1.31	0.6649
	rs11022825	0.20	0.19	0.94	0.62 - 1.41	0.7496	0.17	0.25	1.69	1.15 - 2.46	0.0079
CLOCK	rs6850524	0.42	0.44	1.08	0.79 - 1.5	0.6247	0.45	0.36	0.72	0.52 - 0.98	0.0372
	rs2087319	0.25	0.22	0.86	0.59 - 1.26	0.4313	0.23	0.27	1.23	0.87 - 1.75	0.2442
CRY1	rs7974499	0.47	0.45	0.91	0.65 - 1.26	0.5521	0.46	0.54	1.38	1.01 - 1.89	0.0415
	rs4640029	0.43	0.42	0.94	0.67 - 1.31	0.7102	0.43	0.50	1.28	0.95 - 1.74	0.1043
	rs714359	0.22	0.24	1.12	0.77 - 1.62	0.5679	0.23	0.22	0.94	0.64 - 1.38	0.7523
	rs2287161	0.49	0.44	0.84	0.58 - 1.21	0.3429					
	rs1056560	0.43	0.45	1.08	0.78 - 1.5	0.6379	0.41	0.49	1.47	1.06 - 2.02	0.0195
	rs8192440	0.36	0.39	1.12	0.81 - 1.56	0.5021	0.35	0.47	1.79	1.29 - 2.48	0.0005
	rs10778528	0.41	0.42	1.07	0.78 - 1.48	0.6636	0.38	0.49	1.61	1.16 - 2.22	0.0038
	rs10778533	0.17	0.16	0.95	0.62 - 1.45	0.8161	0.16	0.23	1.56	1.05 - 2.3	0.0289
	rs1921141	0.39	0.38	0.96	0.69 - 1.35	0.8331	0.40	0.33	0.72	0.52 - 1	0.0437
	rs2204830	0.09	0.12	1.33	0.82 - 2.15	0.2647	0.08	0.09	1.08	0.62 - 1.89	0.7913
	rs11113198	0.49	0.52	1.16	0.84 - 1.59	0.3694	0.50	0.46	0.86	0.63 - 1.17	0.3278
	rs4432103	0.34	0.30	0.84	0.59 - 1.2	0.323852	0.32	0.42	1.58	1.14 - 2.18	0.0056
CRY2	rs1139266	0.22	0.35	2.00	1.34 - 3.01	0.0010					
	rs7951225	0.19	0.26	1.59	1.1 - 2.29	0.0156	0.20	0.21	1.04	0.7 - 1.53	0.8536
CSNK1E	rs9610926	0.29	0.32	1.17	0.83 - 1.64	0.3791	0.31	0.32	1.02	0.74 - 1.4	0.9013
	rs135715	0.40	0.41	1.06	0.77 - 1.45	0.7338	0.40	0.36	0.84	0.61 - 1.14	0.2497
	rs9622771	0.17	0.19	1.15	0.76 - 1.73	0.5122	0.17	0.15	0.85	0.57 - 1.28	0.4329
	rs1997644	0.46	0.46	1.04	0.75 - 1.44	0.8304	0.48	0.50	1.13	0.82 - 1.55	0.4521
	rs13054361	0.08	0.04	0.42	0.18 - 0.97	0.0214	0.07	0.08	1.01	0.56 - 1.82	0.9845
	rs763220	0.08	0.15	2.19	1.28 - 3.76	0.0063	0.07	0.08	1.27	0.68 - 2.37	0.4612
	rs5757058	0.49	0.54	1.23	0.88 - 1.73	0.2307	0.50	0.54	1.23	0.89 - 1.7	0.2137
NPAS2	rs10194413	0.09	0.07	0.82	0.44 - 1.54	0.5345	0.10	0.11	1.20	0.72 - 2	0.5011
	rs356652	0.08	0.08	1.01	0.56 - 1.81	0.9829	0.10	0.14	1.49	0.94 - 2.36	0.0987
	rs12712085	0.43	0.34	0.66	0.47 - 0.92	0.01344	0.45	0.47	1.09	0.8 - 1.49	0.5701
	rs3820787	0.37	0.27	0.62	0.44 - 0.89	0.0078	0.36	0.43	1.30	0.93 - 1.81	0.1225
	rs876060	0.22	0.22	1.03	0.69 - 1.56	0.8738	0.22	0.19	0.80	0.53 - 1.2	0.2726
	rs6738097	0.14	0.15	1.07	0.68 - 1.68	0.7822	0.16	0.10	0.60	0.36 - 1	0.0386
	rs4851392	0.28	0.20	0.61	0.41 - 0.92	0.0134	0.29	0.36	1.36	0.97 - 1.9	0.0762
	rs6719437	0.34	0.34	1.02	0.73 - 1.43	0.9179	0.31	0.32	1.04	0.74 - 1.45	0.8269
	rs11123857	0.28	0.36	1.47	1.06 - 2.05	0.0236	0.28	0.23	0.79	0.55 - 1.14	0.2057
	rs1053096	0.34	0.30	0.81	0.58 - 1.15	0.2320	0.33	0.37	1.13	0.82 - 1.56	0.4516
	rs935401	0.43	0.51	1.36	0.99 - 1.87	0.0552	0.44	0.38	0.78	0.56 - 1.07	0.1167
	rs10934	0.28	0.32	1.20	0.86 - 1.67	0.2892	0.30	0.26	0.80	0.56 - 1.14	0.2096
	rs11695176	0.16	0.14	0.81	0.52 - 1.27	0.3542	0.16	0.15	0.91	0.58 - 1.41	0.6582
	rs746924	0.35	0.31	0.84	0.6 - 1.17	0.2953	0.33	0.39	1.23	0.9 - 1.69	0.1969
	rs4850956	0.50	0.48	0.93	0.68 - 1.26	0.6305	0.48	0.51	1.11	0.82 - 1.51	0.5007
	rs12472882	0.28	0.32	1.21	0.87 - 1.68	0.2676	0.30	0.26	0.80	0.56 - 1.14	0.2082
PER1	rs3809881	0.43	0.40	0.88	0.64 - 1.21	0.4347	0.38	0.35	0.84	0.6 - 1.17	0.3094
	rs8067165	0.39	0.37	0.94	0.68 - 1.3	0.7283	0.39	0.38	0.97	0.7 - 1.34	0.8517
	rs3027267	0.09	0.04	0.43	0.19 - 1	0.0286	0.07	0.09	1.33	0.73 - 2.39	0.3615
PER2	hCV27848035	0.14	0.08	0.52	0.29 - 0.92	0.0146	0.16	0.14	0.83	0.53 - 1.29	0.3966
	rs11894535	0.22	0.13	0.52	0.32 - 0.85	0.0050	0.23	0.25	1.04	0.7 - 1.54	0.8402
	rs2304674	0.27	0.19	0.63	0.42 - 0.93	0.0167	0.28	0.28	0.92	0.65 - 1.3	0.6281
	rs2304673	0.14	0.08	0.52	0.29 - 0.92	0.0133	0.15	0.14	0.86	0.55 - 1.33	0.4821
PER3	rs1417986	0.37	0.42	1.27	0.91 - 1.77	0.1645	0.37	0.45	1.32	0.96 - 1.8	0.0849
	rs2066293	0.28	0.28	1.02	0.71 - 1.47	0.8989	0.29	0.38	1.38	1.01 - 1.9	0.0479
	rs707455	0.43	0.34	0.68	0.49 - 0.95	0.0229	0.44	0.46	1.09	0.8 - 1.48	0.5893
	rs1773157	0.16	0.19	1.33	0.88 - 2.02	0.1833	0.15	0.18	1.12	0.76 - 1.66	0.5675
	rs697673	0.22	0.25	1.20	0.82 - 1.75	0.3574	0.23	0.23	0.91	0.63 - 1.32	0.6164
	rs1048785	0.12	0.13	1.06	0.66 - 1.71	0.8017	0.11	0.10	0.91	0.54 - 1.52	0.7129
	rs697686	0.37	0.26	0.61	0.42 - 0.88	0.0071	0.35	0.39	1.17	0.85 - 1.61	0.3249
	rs875994	0.17	0.16	0.98	0.64 - 1.49	0.9249	0.16	0.13	0.80	0.52 - 1.25	0.3181
	rs12141033	0.39	0.29	0.64	0.45 - 0.91	0.0119	0.38	0.45	1.29	0.94 - 1.77	0.1184
	rs10462020	0.18	0.19	1.03	0.69 - 1.54	0.8831	0.18	0.14	0.77	0.5 - 1.19	0.2228
	rs17374439	0.18	0.19	1.03	0.69 - 1.54	0.8853	0.18	0.14	0.77	0.51 - 1.18	0.2226
	rs12741937	0.16	0.11	0.60	0.36 - 1	0.0384	0.15	0.16	1.06	0.69 - 1.64	0.7897
	rs12731471	0.12	0.08	0.69	0.38 - 1.26	0.2046	0.10	0.10	0.97	0.55 - 1.69	0.9005
	rs707476	0.32	0.41	1.45	1.04 - 2.01	0.0289	0.31	0.31	0.97	0.69 - 1.35	0.8458
	rs531485	0.22	0.28	1.41	0.97 - 2.04	0.0764	0.21	0.19	0.88	0.58 - 1.32	0.5222
	rs12566535	0.10	0.05	0.44	0.21 - 0.95	0.0180	0.12	0.12	0.97	0.58 - 1.6	0.8997

Table 4. Summary of variants in circadian genes and their associations with serum androgens and sex hormone-binding globulin (SHBG)

		# SNPs associated with Testosterone at p<0.05			# SNPs associated with 3α Diol G at p<0.05			# SNPs associated with SHBG at p<0.05		
		All controls	Finasteride controls		All controls	Finasteride controls		All controls	Finasteride controls	
Gene	# SNPs Genotyped	Baseline	Follow-up	% Change	Baseline	Follow-up	% Change	Baseline	Follow-up	% Change
ARNTL	28	0	0	0	2	2	3	0	0	4
CLOCK	14	0	7	0	0	0	0	3	0	5
CRY1	22	0	3	2	0	1	0	0	0	0
CRY2	16	4	0	1	0	0	0	0	2	1
CSNK1E	23	1	0	2	2	2	0	4	3	1
NPAS2	79	2	2	12	3	5	4	3	12	2
PER1	17	2	1	1	0	2	0	1	0	1
PER2	24	2	2	1	3	2	0	0	3	3
PER3	30	1	1	0	5	0	0	1	1	0
TIMELESS	2	0	0	0	0	0	0	0	0	1
Total	*255*	*12*	*16*	*19*	*15*	*14*	*7*	*12*	*21*	*18*

Table 5. Correlation between SNPs in circadian genes and serum androgens and SHBG with P-value <0.05 in the PCPT nested case-control study

	P<0.01			Testosterone									3α Diol G									Sex Hormone-Binding Globulin (SHBG)								
	P<0.05			All Controls			Finasteride Group Controls						All Controls			Finasteride Group Controls						All Controls			Finasteride Group Controls					
				Baseline			Follow-up			Percent Change			Baseline			Follow-up			Percent Change			Baseline			Follow-up			Percent Change		
Gene	SNP	Chr	Location	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value
ARNTL	rs12421920	11	13249759	-7.70	-26.63, 11.22	0.4252	-2.89	-37.89, 32.11	0.8713	-1.53	-9.6, 6.54	0.7102	0.05	-0.03, 0.13	0.2095	-0.28	-0.47, -0.09	0.0036	-0.19	-0.36, -0.03	0.0222	0.02	-0.03, 0.08	0.4199	0.05	-0.04, 0.14	0.2671	-0.02	-0.08, 0.03	0.3621
	rs6486121	11	13355770	-0.69	-12.27, 10.89	0.9068	-0.04	-21.16, 21.08	0.9970	-2.59	-7.43, 2.25	0.2954	-0.05	-0.1, 0	0.0702	0.11	-0.01, 0.22	0.0665	0.12	0.02, 0.22	0.0214	0.01	-0.03, 0.04	0.7161	0.00	-0.05, 0.06	0.8631	-0.01	-0.04, 0.02	0.4565
	rs1026071	11	13364712	0.54	-11.6, 12.68	0.9306	0.73	-20.96, 22.41	0.9476	-3.27	-8.26, 1.71	0.1991	-0.05	-0.11, 0	0.0426	0.11	-0.01, 0.22	0.0699	0.13	0.02, 0.23	0.0152	0.03	0, 0.06	0.0904	0.02	-0.03, 0.08	0.3990	-0.02	-0.06, 0.01	0.1833
	rs3789327	11	13385316	5.60	-5.18, 16.37	0.3087	-5.79	-25.2, 13.62	0.5592	0.32	-4.16, 4.79	0.8890	-0.05	-0.1, -0.01	0.0263	-0.06	-0.17, 0.04	0.2397	-0.03	-0.12, 0.07	0.5746	0.00	-0.03, 0.03	0.9425	0.02	-0.03, 0.07	0.3592	0.03	0, 0.06	0.0260
	rs11022785	11	13411534	-4.97	-20.06, 10.12	0.5184	12.55	-13.51, 38.61	0.3456	0.99	-5.02, 7	0.7471	0.03	-0.03, 0.1	0.3160	0.12	-0.02, 0.26	0.0950	-0.01	-0.13, 0.12	0.9161	0.01	-0.03, 0.05	0.7062	-0.01	-0.08, 0.05	0.6878	-0.04	-0.08, 0	0.0421
	rs3761862	11	13424506	-6.07	-22.21, 10.07	0.4612	-12.09	-39.52, 15.34	0.3883	4.67	-1.64, 10.97	0.1478	-0.04	-0.11, 0.03	0.2701	-0.10	-0.25, 0.04	0.1699	-0.05	-0.18, 0.08	0.4439	-0.03	-0.08, 0.01	0.1549	0.02	-0.05, 0.09	0.5232	0.06	0.02, 0.1	0.0041
	rs7103068	11	13429961	-0.44	-11.72, 10.84	0.9385	6.01	-14.28, 26.31	0.5617	-0.59	-5.27, 4.09	0.8054	0.01	-0.04, 0.06	0.7207	0.15	0.04, 0.26	0.0066	0.05	-0.04, 0.15	0.2700	0.00	-0.03, 0.04	0.8193	-0.01	-0.06, 0.04	0.6484	0.00	-0.03, 0.03	0.8679
	rs876226	11	13441444	-2.47	-13.24, 8.3	0.6533	-1.61	-20.91, 17.69	0.8701	0.72	-3.72, 5.17	0.7505	-0.02	-0.06, 0.03	0.4589	0.07	-0.03, 0.18	0.1628	0.02	-0.07, 0.11	0.6286	-0.01	-0.05, 0.02	0.3459	0.00	-0.05, 0.05	0.8815	0.03	0, 0.06	0.0420
CLOCK	rs491381	4	56274764	1.50	-11.49, 14.5	0.8206	4.41	-19.12, 27.94	0.7136	-0.33	-5.75, 5.1	0.9063	0.01	-0.05, 0.07	0.7284	-0.05	-0.18, 0.08	0.4477	-0.03	-0.15, 0.08	0.5564	0.02	-0.01, 0.06	0.2040	0.01	-0.05, 0.07	0.8268	-0.04	-0.08, -0.01	0.0164
	rs13120134	4	56281320	7.83	-4.28, 19.93	0.2053	24.46	1.96, 46.96	0.0337	-0.21	-5.43, 5	0.9362	-0.01	-0.06, 0.04	0.7455	0.03	-0.1, 0.15	0.6769	0.06	-0.05, 0.16	0.2920	0.01	-0.02, 0.05	0.4953	0.03	-0.03, 0.09	0.2678	0.00	-0.03, 0.04	0.9607
	rs1801260	4	56301369	-11.62	-23.97, 0.74	0.0656	-25.99	-47.39, -4.58	0.0178	-3.23	-8.18, 1.73	0.2029	0.02	-0.03, 0.07	0.4885	0.05	-0.06, 0.17	0.3579	0.00	-0.11, 0.1	0.9271	-0.04	-0.07, 0	0.0387	-0.01	-0.07, 0.04	0.6219	0.04	0, 0.07	0.0278
	rs3792603	4	56302058	-5.30	-15.41, 4.81	0.3042	-19.39	-37.4, -1.39	0.0354	-2.74	-7.02, 1.55	0.2122	0.02	-0.02, 0.06	0.3992	0.02	-0.08, 0.12	0.6705	0.04	-0.05, 0.12	0.4016	-0.02	-0.05, 0.01	0.1328	0.00	-0.05, 0.04	0.8907	0.02	0, 0.05	0.0800
	rs11932595	4	56323597	-8.48	-19.49, 2.52	0.1310	-24.76	-43.75, -5.77	0.0110	-4.26	-8.65, 0.14	0.0583	0.00	-0.04, 0.05	0.8571	0.09	-0.01, 0.19	0.0920	0.03	-0.06, 0.12	0.4951	-0.02	-0.05, 0.01	0.1558	-0.03	-0.07, 0.02	0.3224	0.03	0, 0.06	0.0400
	rs2070062	4	56355598	-11.83	-24.2, 0.54	0.0611	-25.99	-47.39, -4.58	0.0178	-3.23	-8.18, 1.73	0.2029	0.02	-0.03, 0.07	0.4745	0.05	-0.06, 0.17	0.3579	0.00	-0.11, 0.1	0.9271	-0.04	-0.07, 0	0.0334	-0.01	-0.07, 0.04	0.6219	0.04	0, 0.07	0.0278
	rs2101476	4	56445128	-11.69	-24, 0.62	0.0629	-25.46	-46.64, -4.28	0.0190	-3.11	-8.02, 1.79	0.2143	0.02	-0.03, 0.07	0.4772	0.05	-0.06, 0.17	0.3641	0.00	-0.11, 0.1	0.9250	-0.04	-0.07, 0	0.0347	-0.02	-0.07, 0.04	0.5475	0.03	0, 0.07	0.0491
	rs2412664	4	56457387	-8.66	-21.83, 4.52	0.1981	-30.22	-53.05, -7.39	0.0098	-3.79	-8.94, 1.37	0.1510	0.04	-0.02, 0.09	0.2221	0.08	-0.05, 0.2	0.2287	0.04	-0.07, 0.15	0.4366	-0.03	-0.07, 0	0.0829	-0.02	-0.08, 0.04	0.5085	0.02	-0.01, 0.06	0.1694
CRY1	rs10861683	12	107381560	-2.19	-14.41, 10.02	0.7248	-11.38	-33.89, 11.13	0.3223	-8.66	-13.8, -3.53	0.00102	-0.02	-0.07, 0.04	0.5183	0.03	-0.1, 0.15	0.6735	0.04	-0.07, 0.14	0.5001	0.02	-0.02, 0.05	0.2974	0.05	-0.01, 0.11	0.1028	-0.02	-0.06, 0.01	0.2115
	rs12368868	12	107405591	-13.36	-31, 4.28	0.1381	-42.44	-76.6, -8.29	0.0153	-3.86	-11.8, 4.08	0.3413	0.01	-0.06, 0.09	0.7178	-0.08	-0.27, 0.1	0.3784	-0.14	-0.3, 0.03	0.1004	-0.02	-0.07, 0.03	0.5035	-0.05	-0.14, 0.04	0.3079	-0.02	-0.07, 0.03	0.4682
	rs11113179	12	107452785	-14.10	-31.61, 3.42	0.1149	-43.46	-77.06, -9.85	0.0116	-3.28	-11.08, 4.52	0.4101	0.02	-0.06, 0.09	0.6543	-0.07	-0.25, 0.12	0.4746	-0.14	-0.3, 0.02	0.0852	-0.02	-0.07, 0.03	0.4151	-0.04	-0.13, 0.04	0.3170	-0.01	-0.07, 0.04	0.5711
	rs12315175	12	107499272	7.99	-5.37, 21.35	0.2415	28.27	4.28, 52.26	0.0214	5.99	0.46, 11.53	0.0345	-0.02	-0.08, 0.03	0.4317	-0.02	-0.16, 0.11	0.7082	0.02	-0.09, 0.13	0.7379	-0.01	-0.05, 0.03	0.6230	0.00	-0.06, 0.06	0.9431	0.00	-0.04, 0.04	0.9974
	rs2204830	12	107527163	0.53	-17.64, 18.7	0.9545	-6.32	-42.21, 29.57	0.7302	-1.10	-9.37, 7.17	0.7945	0.07	0, 0.15	0.0633	0.19	0, 0.39	0.0486	0.05	-0.12, 0.21	0.6010	-0.02	-0.07, 0.04	0.5627	-0.06	-0.16, 0.03	0.1856	0.00	-0.05, 0.06	0.8773
CRY2	rs11823366	11	45828332	-19.73	-39.32, -0.14	0.0486	-8.75	-46.38, 28.88	0.6487	5.20	-3.46, 13.86	0.2395	-0.06	-0.14, 0.03	0.1857	-0.04	-0.24, 0.17	0.7179	0.00	-0.18, 0.18	0.9820	0.00	-0.05, 0.06	0.9739	-0.01	-0.1, 0.09	0.8850	0.01	-0.04, 0.07	0.6104
	rs1139266	11	45832935	-15.73	-30.73, -0.74	0.0400							0.01	-0.06, 0.07	0.8814							-0.04	-0.08, 0.01	0.0891						
	rs11607883	11	45839709	-11.68	-22.81, -0.55	0.0400	-12.93	-33.28, 7.42	0.2137	2.02	-2.67, 6.7	0.4001	-0.03	-0.08, 0.02	0.2552	-0.04	-0.15, 0.07	0.4671	-0.05	-0.15, 0.05	0.2999	-0.03	-0.06, 0.01	0.1022	-0.05	-0.1, 0	0.0661	-0.01	-0.04, 0.02	0.5092
	rs7121775	11	45864323	-5.04	-17.77, 7.68	0.4376	-7.93	-31.45, 15.59	0.5090	1.77	-3.66, 7.19	0.5238	-0.02	-0.08, 0.03	0.4655	-0.01	-0.13, 0.12	0.9183	-0.01	-0.12, 0.1	0.8441	-0.01	-0.05, 0.02	0.4592	-0.06	-0.13, 0	0.0381	-0.02	-0.06, 0.01	0.2060
	rs2292910	11	45903613	-12.96	-24.71, -1.22	0.0307	-13.34	-34.76, 8.07	0.2228	2.74	-2.19, 7.68	0.2768	-0.02	-0.07, 0.03	0.5090	-0.02	-0.13, 0.1	0.7525	-0.03	-0.13, 0.08	0.6146	-0.02	-0.05, 0.02	0.3145	-0.06	-0.11, 0	0.0337	-0.01	-0.05, 0.02	0.3782
	rs1554338	11	45906830	-6.59	-29.52, 16.34	0.5736	8.09	-32.24, 48.42	0.6944	13.37	4.23, 22.52	0.0044	-0.05	-0.15, 0.05	0.3476	0.02	-0.2, 0.24	0.8291	0.02	-0.17, 0.21	0.8500	0.03	-0.04, 0.09	0.4021	0.01	-0.09, 0.11	0.8494	0.03	-0.03, 0.09	0.3635
CSNK1E	rs6001074	22	38655597	-2.30	-13.68, 9.08	0.6920	2.39	-18.73, 23.51	0.8247	3.55	-1.31, 8.41	0.1528	-0.01	-0.06, 0.04	0.6573	-0.10	-0.21, 0.01	0.0867	-0.01	-0.11, 0.09	0.7770	0.02	-0.01, 0.05	0.2496	-0.02	-0.07, 0.04	0.4929	-0.04	-0.07, -0.01	0.0192
	rs135715	22	38660871	-6.70	-17.51, 4.11	0.2249	-15.32	-34.7, 4.07	0.1223	-4.89	-9.35, -0.42	0.0326	0.01	-0.03, 0.06	0.5893	0.03	-0.08, 0.13	0.6267	-0.02	-0.11, 0.07	0.6261	-0.01	-0.04, 0.02	0.3761	0.01	-0.04, 0.06	0.6178	0.03	0, 0.06	0.0639
	rs12485196	22	38662396	16.85	3, 30.71	0.0173	11.47	-13.22, 36.17	0.3631	0.49	-5.25, 6.23	0.8682	-0.01	-0.07, 0.05	0.7075	0.06	-0.07, 0.19	0.3767	0.06	-0.05, 0.18	0.2988	0.01	-0.03, 0.05	0.5710	0.00	-0.07, 0.06	0.9358	0.01	-0.03, 0.04	0.7941
	rs1997644	22	38715222	-10.00	-21.08, 1.07	0.0770	-9.24	-29.29, 10.8	0.3667	3.57	-1.05, 8.2	0.1307	0.01	-0.04, 0.05	0.7805	0.05	-0.06, 0.16	0.3704	0.03	-0.07, 0.12	0.5406	-0.04	-0.07, -0.01	0.0116	-0.07	-0.12, -0.02	0.0090	0.03	0, 0.06	0.0949
	rs5995570	22	38724132	-11.63	-23.79, 0.52	0.0610	-7.26	-29.47, 14.95	0.5221	3.58	-1.39, 8.55	0.1592	-0.01	-0.07, 0.04	0.6186	0.04	-0.08, 0.16	0.5389	0.02	-0.08, 0.13	0.6766	-0.03	-0.07, 0	0.0438	-0.06	-0.11, 0	0.0408	0.02	-0.02, 0.05	0.3437
	rs13054361	22	38732824	-7.68	-27.13, 11.76	0.4389	-2.40	-36.98, 32.19	0.8920	8.81	0.88, 16.73	0.0300	0.04	-0.05, 0.12	0.3653	0.01	-0.18, 0.19	0.9548	-0.02	-0.18, 0.14	0.8087	-0.06	-0.11, 0	0.0482	-0.03	-0.12, 0.06	0.5105	0.01	-0.04, 0.07	0.6060
	rs5757055	22	38740853	6.41	-4.84, 17.66	0.2646	4.18	-16.56, 24.91	0.6933	-1.05	-5.89, 3.79	0.6705	-0.04	-0.09, 0.01	0.0892	-0.05	-0.16, 0.06	0.3830	-0.01	-0.11, 0.09	0.8394	0.04	0.01, 0.07	0.0181	0.06	0, 0.11	0.0415	0.00	-0.03, 0.03	0.9937
	rs5750597	22	38741793	10.35	-6.23, 26.93	0.2214	22.46	-8.16, 53.07	0.1513	0.82	-6.01, 7.65	0.8146	0.10	0.03, 0.17	0.0076	0.22	0.05, 0.38	0.0094	0.05	-0.09, 0.2	0.4597	0.00	-0.04, 0.05	0.9244	0.03	-0.05, 0.11	0.4065	0.00	-0.05, 0.05	0.9666
	rs6001098	22	38743302	7.83	-5.26, 20.92	0.2413	11.79	-13, 36.59	0.3518	5.01	-0.68, 10.69	0.0854	0.09	0.04, 0.15	0.0014	0.15	0.01, 0.28	0.0323	0.03	-0.08, 0.15	0.5585	0.00	-0.04, 0.03	0.8639	0.01	-0.06, 0.07	0.8435	-0.01	-0.04, 0.03	0.7548
NPAS2	rs7565018	2	101397139	4.42	-8.76, 17.6	0.5110	-15.08	-38.04, 7.88	0.1987	0.21	-5.27, 5.69	0.9398	-0.02	-0.07, 0.04	0.6030	0.03	-0.1, 0.16	0.6485	0.05	-0.06, 0.16	0.3498	-0.02	-0.06, 0.02	0.2806	-0.07	-0.12, -0.01	0.0306	0.00	-0.03, 0.04	0.9234
	rs6740234	2	101408323	2.41	-11.25, 16.08	0.7293	-18.27	-42.56, 6.02	0.1412	-0.38	-5.99, 5.23	0.8946	0.00	-0.06, 0.06	0.9444	0.05	-0.08, 0.19	0.4185	0.04	-0.07, 0.16	0.4478	-0.02	-0.06, 0.02	0.2829	-0.07	-0.13, 0	0.0395	0.01	-0.03, 0.04	0.7584
	rs17024814	2	101426316	2.22	-20, 24.44	0.8448	13.13	-25.83, 52.09	0.5093	2.48	-6.5, 11.46	0.5886	-0.03	-0.13, 0.06	0.4853	0.13	-0.08, 0.34	0.2152	0.20	0.02, 0.39	0.0289	-0.03	-0.09, 0.03	0.3420	-0.04	-0.14, 0.06	0.4289	0.00	-0.06, 0.06	0.9476
	rs17024869	2	101460043	8.94	-10.19, 28.07	0.3598	9.91	-25.04, 44.85	0.5787	-8.15	-16.17, -0.13	0.0472	0.03	-0.06, 0.11	0.5274	0.14	-0.05, 0.33	0.1632	0.00	-0.17, 0.17	0.9884	-0.04	-0.1, 0.01	0.1051	-0.03	-0.12, 0.06	0.4671	-0.03	-0.09, 0.02	0.2356
	rs7557936	2	101460446	4.10	-8.23, 16.43	0.5149	-27.71	-49.74, -5.69	0.0141	-5.78	-10.86, -0.69	0.0264	0.05	0, 0.1	0.0686	0.05	-0.07, 0.17	0.4361	-0.04	-0.15, 0.06	0.3999	-0.02	-0.05, 0.02	0.3063	-0.07	-0.13, -0.02	0.0137	-0.01	-0.05, 0.02	0.3956
	rs7598826	2	101473434	3.82	-7.29, 14.92	0.5009	-8.56	-28.01, 10.88	0.3887	-1.31	-5.79, 3.17	0.5673	0.06	0.01, 0.11	0.0109	0.11	0.01, 0.22	0.0364	-0.01	-0.1, 0.08	0.8567	0.00	-0.03, 0.03	0.9986	-0.06	-0.11, -0.01	0.0148	-0.02	-0.05, 0	0.1003
	rs983287	2	101480401	10.14	-3.07, 23.35	0.1327	-14.46	-37.52, 8.59	0.2196	-6.05	-11.35, -0.76	0.0255	0.05	0, 0.11	0.0615	0.08	-0.04, 0.21	0.1903	-0.02	-0.13, 0.09	0.6969	-0.01	-0.05, 0.03	0.5856	-0.05	-0.11, 0.01	0.0763	-0.02	-0.05, 0.02	0.3168
	rs2871389	2	101495174	1.46	-10.39, 13.32	0.8090	-16.55	-37.61, 4.5	0.1241	-4.91	-9.76, -0.07	0.0476	0.04	-0.01, 0.09	0.1035	0.08	-0.04, 0.19	0.1912	-0.03	-0.13, 0.07	0.5485	-0.03	-0.07, 0	0.0584	-0.06	-0.12, -0.01	0.0218	-0.02	-0.05, 0.01	0.2715
	rs6723452	2	101505074	1.61	-10.54, 13.77	0.7947	17.78	-4.28, 39.84	0.1149	1.32	-3.78, 6.42	0.6122	-0.06	-0.11, 0	0.0371	-0.06	-0.18, 0.06	0.3618	0.03	-0.07, 0.13	0.5658	0.00	-0.03, 0.04	0.9485	0.07	0.01, 0.12	0.0220	0.03	-0.01, 0.06	0.1019
	rs6740935	2	101506423	-1.95	-14.03, 10.12	0.7515	12.77	-9.44, 34.97	0.2605	5.19	0.24, 10.13	0.0405	-0.01	-0.06, 0.05	0.8127	-0.04	-0.16, 0.08	0.5274	-0.03	-0.13, 0.08	0.6104	0.01	-0.02, 0.05	0.5161	0.02	-0.04, 0.08	0.4869	0.02	-0.01, 0.06	0.1930
	rs2117714	2	101521777	-3.03	-16.74, 10.68	0.6650	3.67	-21.14, 28.48	0.7720	8.63	2.86, 14.39	0.0036	0.03	-0.03, 0.09	0.2834	0.09	-0.05, 0.23	0.2171	0.05	-0.07, 0.17	0.4296	0.00	-0.04, 0.04	0.9470	-0.05	-0.12, 0.01	0.1017	0.01	-0.03, 0.05	0.6485
	rs4851377	2	101522266	-7.87	-18.95, 3.2	0.1639	-11.73	-31.52, 8.06	0.2460	5.22	0.67, 9.76	0.0250	0.05	0, 0.09	0.0639	0.06	-0.05, 0.16	0.3037	0.01	-0.08, 0.11	0.7755	-0.01	-0.04, 0.03	0.7070	-0.08	-0.13, -0.03	0.0011	-0.02	-0.05, 0.01	0.2110
	rs7570190	2	101528047	-3.66	-18.35, 11.04	0.6258	5.44	-21.1, 31.98	0.6880	7.95	1.82, 14.07	0.0113	0.00	-0.07, 0.06	0.9108	0.05	-0.1, 0.2	0.5063	0.02	-0.11, 0.15	0.7544	0.01	-0.04, 0.05	0.7633	-0.03	-0.1, 0.03	0.3270	0.01	-0.04, 0.05	0.8043
	rs13026599	2	101541270	1.38	-13.13, 15.88	0.8525	-1.55	-28.91, 25.81	0.9116	-6.83	-13.1, -0.56	0.0334	-0.03	-0.09, 0.03	0.3859	-0.10	-0.24, 0.05	0.2044	-0.07	-0.2, 0.06	0.2960	0.00	-0.04, 0.04	0.9634	0.07	0, 0.14	0.0465	0.02	-0.02, 0.06	0.3966
	rs3754674	2	101549761	6.03	-5.16, 17.23	0.2909	19.31	-0.88, 39.51	0.0616	5.20	0.56, 9.85	0.0287	-0.02	-0.07, 0.03	0.4310	-0.04	-0.15, 0.07	0.4821	-0.02	-0.12, 0.08	0.6904	0.03	0, 0.06	0.0854	0.03	-0.02, 0.08	0.2312	0.02	-0.01, 0.05	0.1531
	rs13025524	2	101550181	6.11	-5.65, 17.87	0.3085	13.35	-7.88, 34.58	0.2185	5.69	0.82, 10.56	0.0226	-0.02	-0.07, 0.03	0.4936	-0.04	-0.15, 0.08	0.5180	-0.01	-0.11, 0.09	0.8861	0.02	-0.01, 0.06	0.1948	0.02	-0.04, 0.07	0.5321	0.03	-0.01, 0.06	0.1244
	rs895521	2	101552095	-6.22	-18.71, 6.28	0.3297	-13.15	-35.16, 8.85	0.2421	-0.07	-5.15, 5.01	0.9776	0.06	0, 0.11	0.0403	0.08	-0.04, 0.2	0.1733	-0.02	-0.12, 0.08	0.6975	-0.02	-0.05, 0.02	0.3404	-0.07	-0.13, -0.01	0.0137	-0.02	-0.05, 0.02	0.3770
	rs7605434	2	101558984	-0.09	-17.61, 17.43	0.9921	-29.48	-59.76, 0.8	0.0571	-7.64	-14.61, -0.67	0.0323	0.03	-0.05, 0.1	0.4768	0.14	-0.02, 0.3	0.0913	0.03	-0.11, 0.17	0.6747	-0.02	-0.07, 0.03	0.5481	-0.06	-0.14, 0.02	0.1391	-0.07	-0.12, -0.03	0.0023
	rs12712085	2	101565151	6.65	-4.33, 17.63	0.2353	10.02	-9.71, 29.76	0.3200	0.17	-4.38, 4.72	0.9404	-0.01	-0.06, 0.03	0.5969	-0.11	-0.21, 0	0.0493	-0.11	-0.21, -0.02	0.0153	0.04	0.01, 0.07	0.0097	0.05	0, 0.1	0.0474	-0.01	-0.04, 0.02	0.5058
	rs3820787	2	101566234	8.59	-2.84, 20.03	0.1412	9.78	-11.31, 30.87	0.3641	0.01	-4.85, 4.88	0.9952	-0.03	-0.08, 0.02	0.1775	-0.18	-0.3, -0.07	0.0015	-0.14	-0.24, -0.04	0.0061	0.03	0, 0.06	0.0794	0.05	0, 0.11	0.0657	0.00	-0.04, 0.03	0.7860
	rs4851390	2	101571705	-5.52	-19.09, 8.04	0.4252	-17.86	-40.94, 5.22	0.1302	-3.70	-9.02, 1.62	0.1740	0.00	-0.06, 0.05	0.8746	0.13	0.01, 0.25	0.0417	0.11	0, 0.22	0.0510	-0.04	-0.08, 0	0.0477	-0.06	-0.11, 0	0.0717	0.00	-0.04, 0.03	0.8718
	rs4851392	2	101581976	2.30	-9.86, 14.46	0.7105	16.44	-5.82, 38.71	0.1485	0.74	-4.4, 5.88	0.7778	-0.02	-0.07, 0.03	0.4007	-0.12	-0.24, 0	0.0526	-0.12	-0.23, -0.02	0.0214	0.00	-0.03, 0.04	0.7989	0.05	-0.01, 0.1	0.1239	0.00	-0.04, 0.03	0.9068
	rs2305159	2	101591443	-5.25	-18.37, 7.87	0.4333	-25.96	-49.7, -2.22	0.0328	-2.32	-7.64, 3	0.3932	-0.01	-0.06, 0.05	0.8608	0.07	-0.06, 0.2	0.2955	0.03	-0.08, 0.14	0.5642	0.00	-0.04, 0.04	0.9700	-0.07	-0.13, -0.01	0.0200	-0.03	-0.07, 0	0.0740
	rs1542178	2	101595475	1.87	-9.98, 13.73	0.7571	12.39	-8.98, 33.77	0.2565	-0.04	-4.95, 4.87	0.9878	-0.03	-0.08, 0.03	0.3242	-0.06	-0.17, 0.06	0.3303	-0.05	-0.15, 0.05	0.3608	0.00	-0.03, 0.03	0.9682	0.06	0, 0.11	0.0444	0.01	-0.03, 0.04	0.6686
	rs2278727	2	101598677	-6.03	-19.4, 7.33	0.3766	-13.01	-38.38, 12.35	0.3154	-1.88	-7.49, 3.74	0.5126	0.02	-0.04, 0.07	0.5800	0.17	0.03, 0.3	0.0147	0.08	-0.03, 0.2	0.1663	-0.01	-0.05, 0.03	0.6005	-0.05	-0.12, 0.01	0.1063	-0.03	-0.06, 0.01	0.1776
	rs11123857	2	101603812	-14.25	-26.17, -2.33	0.0193	-13.66	-35.54, 8.23	0.2221	1.05	-4, 6.1	0.6836	0.01	-0.04, 0.06	0.6752	0.04	-0.08, 0.16	0.4948	0.03	-0.07, 0.13	0.5773	-0.03	-0.06, 0.01	0.1402	-0.02	-0.08, 0.03	0.4242	0.03	-0.01, 0.06	0.1084
	rs11695176	2	101623667	14.68	0.52, 28.83	0.0423	17.51	-7.76, 42.78	0.1752	-1.81	-7.65, 4.02	0.5430	0.00	-0.06, 0.06	0.9242	-0.04	-0.17, 0.1	0.5897	-0.01	-0.13, 0.11	0.8373	0.02	-0.02, 0.06	0.4537	0.06	0, 0.13	0.0563	-0.01	-0.05, 0.03	0.4891
	rs17663389	2	101635989	-13.73	-29.6, 2.15	0.0905	-5.70	-35.03, 23.62	0.7032	2.81	-3.95, 9.56	0.4157	0.02	-0.05, 0.09	0.5792	-0.03	-0.18, 0.13	0.7475	-0.01	-0.15, 0.12	0.8396	-0.02	-0.06, 0.03	0.4013	-0.01	-0.09, 0.06	0.7085	0.05	0, 0.09	0.0470
	rs2289951	2	101644299	15.94	-0.38, 32.27	0.0559	9.30	-20.1, 38.7	0.5356	-2.54	-9.32, 4.23	0.4620	0.01	-0.06, 0.08	0.7005	0.05	-0.11, 0.21	0.5418	-0.02	-0.16, 0.12	0.8057	0.05	0, 0.1	0.0387	0.03	-0.04, 0.11	0.3995	0.00	-0.05, 0.04	0.9894

Table 5. Correlation between SNPs in circadian genes and serum Androgens and SHBG with P-value<0.05 in the PCPT nested case-control study (cont.)

	P<0.01			Testosterone									3α Diol G								Sex Hormone-Binding Globulin (SHBG)							
	P<0.05			All Controls			Finasteride Group Controls						All Controls			Finasteride Group Controls						All Controls			Finasteride Group Controls				
				Baseline			Follow-up			Percent Change			Baseline			Follow-up			Percent Change			Baseline			Follow-up			Percent Change		
Gene	SNP	Chr	Location	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value
PER1	rs3809882	17	7999589	13.01	1.64, 24.37	0.0251	21.97	0.39, 43.55	0.0467	-0.10	-5.1, 4.89	0.9679	-0.03	-0.07, 0.02	0.3103	0.02	-0.1, 0.13	0.7749	0.04	-0.06, 0.14	0.4500	0.02	-0.01, 0.05	0.2147	0.05	0, 0.11	0.0535	-0.01	-0.05, 0.02	0.4626
	rs9894356	17	8006312	-13.37	-26.15, -0.58	0.0407	-18.22	-42.57, 6.14	0.1435	-1.77	-7.38, 3.84	0.5372	0.01	-0.04, 0.07	0.6730	0.02	-0.11, 0.15	0.7708	0.00	-0.12, 0.11	0.9559	0.01	-0.03, 0.05	0.5533	-0.03	-0.09, 0.04	0.3936	-0.01	-0.05, 0.03	0.5991
	rs9912048	17	8008535	8.54	-3, 20.09	0.1470	-6.16	-26.49, 14.16	0.5525	-2.71	-7.39, 1.96	0.2565	0.01	-0.04, 0.06	0.7787	0.11	0, 0.22	0.0431	0.05	-0.04, 0.15	0.2644	0.03	0, 0.07	0.0441	-0.04	-0.09, 0.01	0.1329	-0.05	-0.08, -0.02	0.0032
	rs7215658	17	8010164	4.10	-9.35, 17.55	0.5504	6.08	-18.37, 30.54	0.6261	-2.21	-7.84, 3.43	0.4433	-0.02	-0.08, 0.04	0.4643	-0.14	-0.28, -0.01	0.0318	-0.05	-0.16, 0.07	0.4302	0.00	-0.03, 0.04	0.8370	0.02	-0.04, 0.08	0.5309	-0.02	-0.06, 0.02	0.2630
	rs3027267	17	8090895	5.52	-15.07, 26.11	0.5995	-22.57	-58.64, 13.51	0.2210	-10.41	-18.8, -2.01	0.0156	0.03	-0.06, 0.12	0.5134	0.13	-0.06, 0.32	0.1759	0.04	-0.13, 0.2	0.6851	0.01	-0.05, 0.07	0.6751	-0.01	-0.1, 0.08	0.8420	-0.03	-0.08, 0.03	0.3323
PER2	rs7558403	2	239103749	-8.07	-19.51, 3.38	0.1673	-1.62	-22.2, 18.96	0.8777	-0.57	-5.21, 4.06	0.8084	-0.05	-0.1, 0	0.0343	0.03	-0.08, 0.14	0.6050	0.05	-0.05, 0.15	0.3126	-0.03	-0.06, 0	0.0821	-0.02	-0.07, 0.04	0.5722	0.02	-0.01, 0.05	0.1804
	rs4663863	2	239121733	7.12	-5.84, 20.07	0.2821	6.33	-17.59, 30.25	0.6044	-4.12	-9.62, 1.38	0.1430	0.06	0.01, 0.12	0.0251	0.00	-0.13, 0.13	0.9709	-0.06	-0.17, 0.05	0.2938	0.01	-0.03, 0.05	0.6309	0.06	0, 0.12	0.0556	-0.01	-0.05, 0.03	0.6269
	rs6722019	2	239128117	14.76	3.65, 25.87	0.0094	0.74	-19.41, 20.89	0.9426	1.11	-3.53, 5.75	0.6391	0.06	0.01, 0.1	0.0208	0.04	-0.07, 0.15	0.4350	-0.06	-0.15, 0.04	0.2168	0.03	0, 0.06	0.0690	-0.01	-0.06, 0.04	0.6875	-0.03	-0.06, 0	0.0353
	rs2305174	2	239133324	7.06	-9.77, 23.89	0.4112	9.04	-20.79, 38.87	0.5529	3.55	-3.36, 10.46	0.3143	-0.02	-0.1, 0.05	0.5498	-0.16	-0.33, 0	0.0497	-0.06	-0.2, 0.08	0.4118	0.00	-0.05, 0.04	0.9226	0.03	-0.05, 0.11	0.4096	0.00	-0.05, 0.05	0.9508
	rs56386336	2	239153948	-0.55	-15.56, 14.46	0.9427	-28.04	-56.47, 0.39	0.0539	0.28	-6.34, 6.9	0.9340	-0.01	-0.07, 0.06	0.8140	0.08	-0.08, 0.23	0.3331	-0.01	-0.14, 0.13	0.8912	-0.02	-0.06, 0.02	0.3211	-0.09	-0.17, -0.02	0.0132	-0.02	-0.06, 0.02	0.3567
	rs11894535	2	239177073	-7.84	-21.54, 5.87	0.2627	-39.70	-65.93, -13.47	0.0032	0.03	-6.04, 6.1	0.9931	0.02	-0.04, 0.08	0.4760	0.06	-0.08, 0.2	0.4280	-0.02	-0.14, 0.1	0.7646	-0.02	-0.06, 0.02	0.2999	-0.10	-0.17, -0.03	0.0037	-0.02	-0.06, 0.02	0.2406
	rs2304673	2	239185922	-1.93	-17.08, 13.23	0.8031	-32.10	-60.99, -3.21	0.0300	-0.80	-7.49, 5.9	0.8158	0.00	-0.07, 0.06	0.9714	0.08	-0.07, 0.24	0.3070	-0.02	-0.15, 0.12	0.8272	-0.02	-0.06, 0.02	0.3556	-0.09	-0.16, -0.01	0.0264	-0.02	-0.07, 0.02	0.2705
	rs7595976	2	239215744	-0.83	-12.09, 10.42	0.8848	12.99	-7.21, 33.19	0.2082	1.71	-2.96, 6.38	0.4728	0.00	-0.05, 0.05	0.9941	-0.07	-0.18, 0.04	0.1967	0.00	-0.09, 0.1	0.9261	0.00	-0.03, 0.03	0.8776	0.03	-0.02, 0.08	0.2984	0.03	0, 0.06	0.0456
	rs7599697	2	239231477	12.17	0.99, 23.35	0.0331	12.12	-7.8, 32.04	0.2337	-1.19	-5.75, 3.36	0.6084	-0.01	-0.06, 0.04	0.7006	0.06	-0.05, 0.16	0.3194	0.04	-0.06, 0.13	0.4618	0.01	-0.02, 0.05	0.3646	0.03	-0.02, 0.08	0.2149	-0.03	-0.06, 0	0.0756
	rs6737780	2	239235287	-11.22	-23.84, 1.39	0.0815	9.35	-13.57, 32.27	0.4243	5.31	0.03, 10.59	0.0496	0.01	-0.05, 0.06	0.8273	-0.10	-0.23, 0.02	0.0953	-0.05	-0.16, 0.05	0.3344	-0.02	-0.05, 0.02	0.3237	0.00	-0.06, 0.06	0.9332	0.04	0.01, 0.07	0.0236
PER3	rs1417986	1	7797734	-2.39	-13.54, 8.76	0.6744	4.39	-14.96, 23.75	0.6567	-0.64	-5.11, 3.82	0.7774	-0.08	-0.13, -0.03	0.0012	-0.03	-0.14, 0.07	0.5174	0.05	-0.04, 0.14	0.2765	0.00	-0.03, 0.03	0.8935	0.04	-0.01, 0.09	0.1146	0.00	-0.03, 0.03	0.8420
	rs2066293	1	7810543	-4.60	-16.76, 7.55	0.4580	8.37	-12.27, 29.01	0.4272	2.15	-2.63, 6.93	0.3789	-0.08	-0.13, -0.03	0.0020	-0.05	-0.16, 0.07	0.4168	0.03	-0.06, 0.13	0.5019	-0.01	-0.05, 0.02	0.4943	0.04	-0.02, 0.09	0.1949	0.01	-0.03, 0.04	0.7369
	rs2640908	1	7889941	-16.36	-30.65, -2.07	0.0251	-9.45	-34.04, 15.14	0.4518	3.14	-2.52, 8.8	0.2772	-0.06	-0.13, 0	0.0417	-0.07	-0.21, 0.06	0.2703	0.00	-0.12, 0.12	0.9991	-0.03	-0.07, 0.01	0.1686	-0.01	-0.08, 0.05	0.6754	0.02	-0.01, 0.06	0.2143
	rs707476	1	7918106	-6.00	-17.79, 5.8	0.3192	14.84	-6.72, 36.41	0.1781	2.20	-2.78, 7.17	0.3876	-0.05	-0.1, 0	0.0404	-0.08	-0.19, 0.04	0.1982	-0.03	-0.14, 0.07	0.5139	-0.02	-0.05, 0.02	0.3747	0.05	-0.01, 0.1	0.1138	0.03	0, 0.06	0.0817
	rs579992	1	7927981	-4.22	-22.67, 14.22	0.6539	0.63	-33.25, 34.51	0.9711	-1.53	-9.33, 6.27	0.7009	-0.11	-0.19, -0.03	0.0070	-0.06	-0.24, 0.12	0.5277	0.05	-0.11, 0.21	0.5747	-0.03	-0.08, 0.02	0.2677	0.02	-0.06, 0.11	0.5843	0.02	-0.03, 0.07	0.4554
	rs1040397	1	7952427	4.07	-7.29, 15.43	0.4828	20.84	0.31, 41.38	0.0473	1.14	-3.66, 5.94	0.6422	0.02	-0.03, 0.07	0.5007	0.01	-0.1, 0.13	0.8016	-0.02	-0.12, 0.08	0.7451	0.04	0.01, 0.07	0.0103	0.06	0, 0.11	0.0405	0.00	-0.03, 0.04	0.7952
TIMELESS	rs774047	12	56815922	5.22	-5.59, 16.03	0.3439	7.42	-11.97, 26.82	0.4535	-0.03	-4.5, 4.44	0.9891	-0.03	-0.07, 0.02	0.2335	-0.07	-0.17, 0.04	0.2222	-0.03	-0.12, 0.06	0.5082	0.01	-0.02, 0.04	0.4084	0.02	-0.03, 0.07	0.3700	-0.03	-0.06, 0	0.0241

Figure 1. Main effects of individual circadian gene variants on total prostate cancer risk in men in the PCPT by treatment group

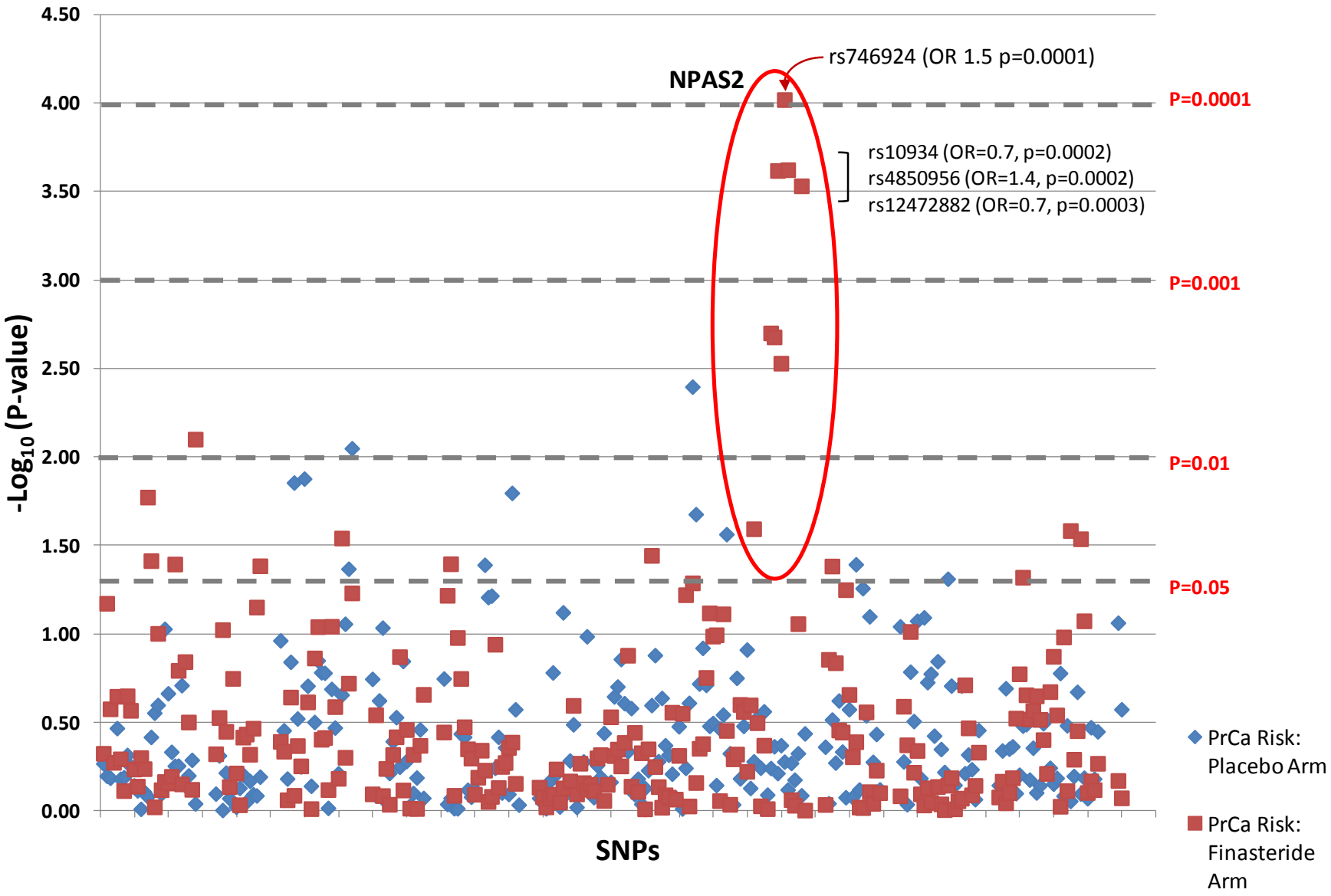

Figure 2. Main effects of individual circadian gene variants on low-grade prostate cancer risk in the PCPT by treatment group

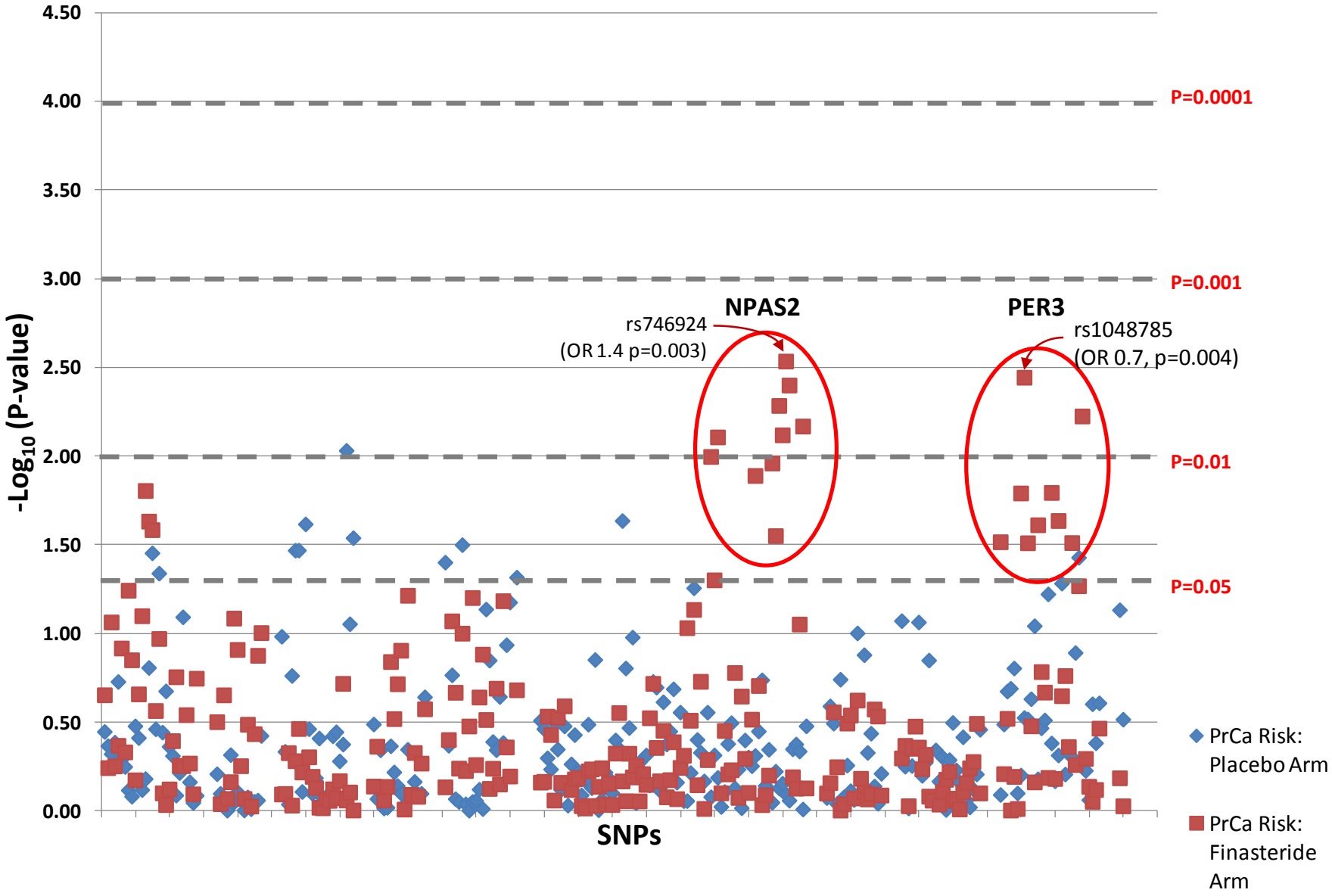

Figure 3. Main effects of individual circadian gene variants on high-grade prostate cancer risk in the PCPT by treatment group

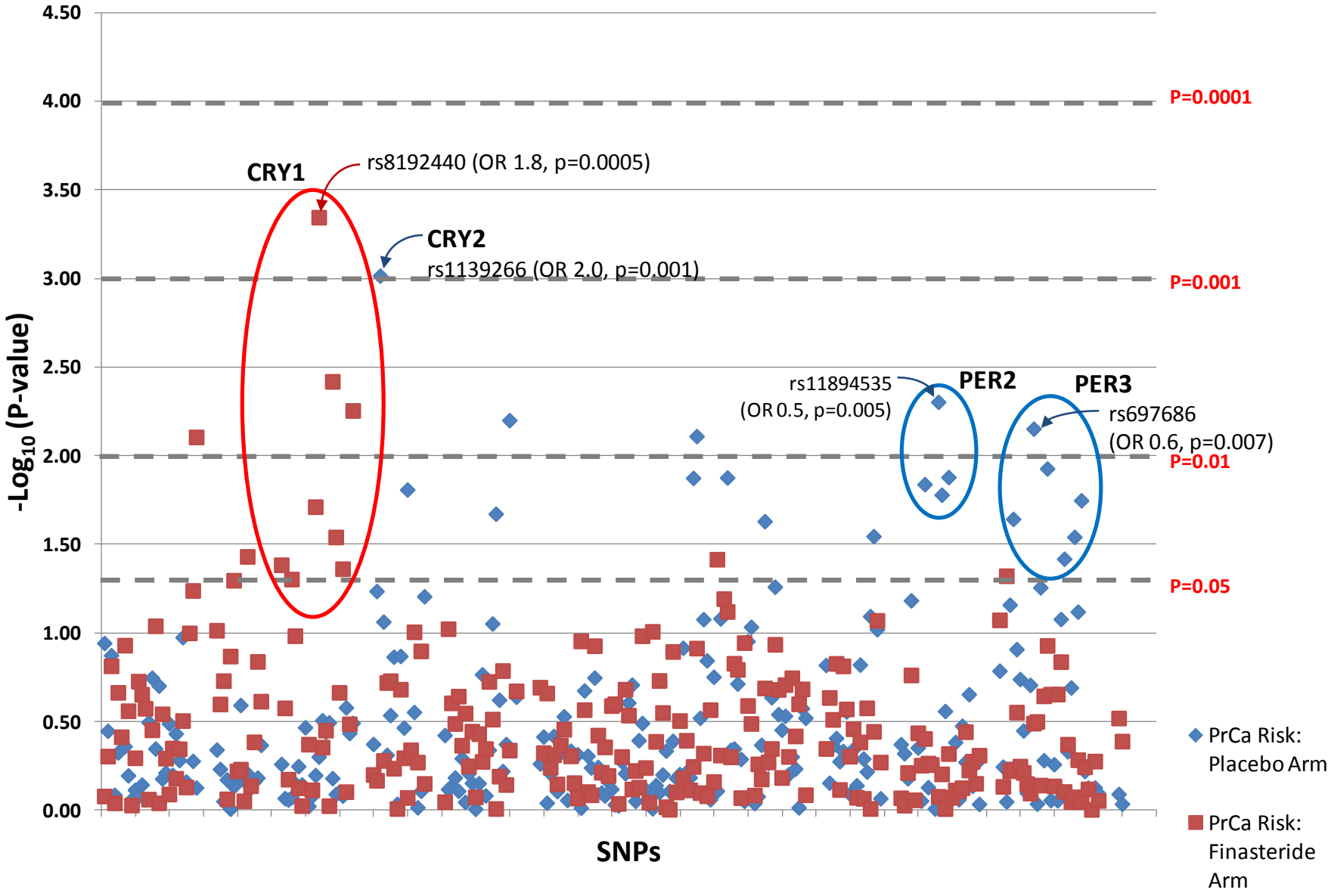

Figure 4. Correlation between individual circadian gene variants on total serum testosterone levels in the finasteride-treated men

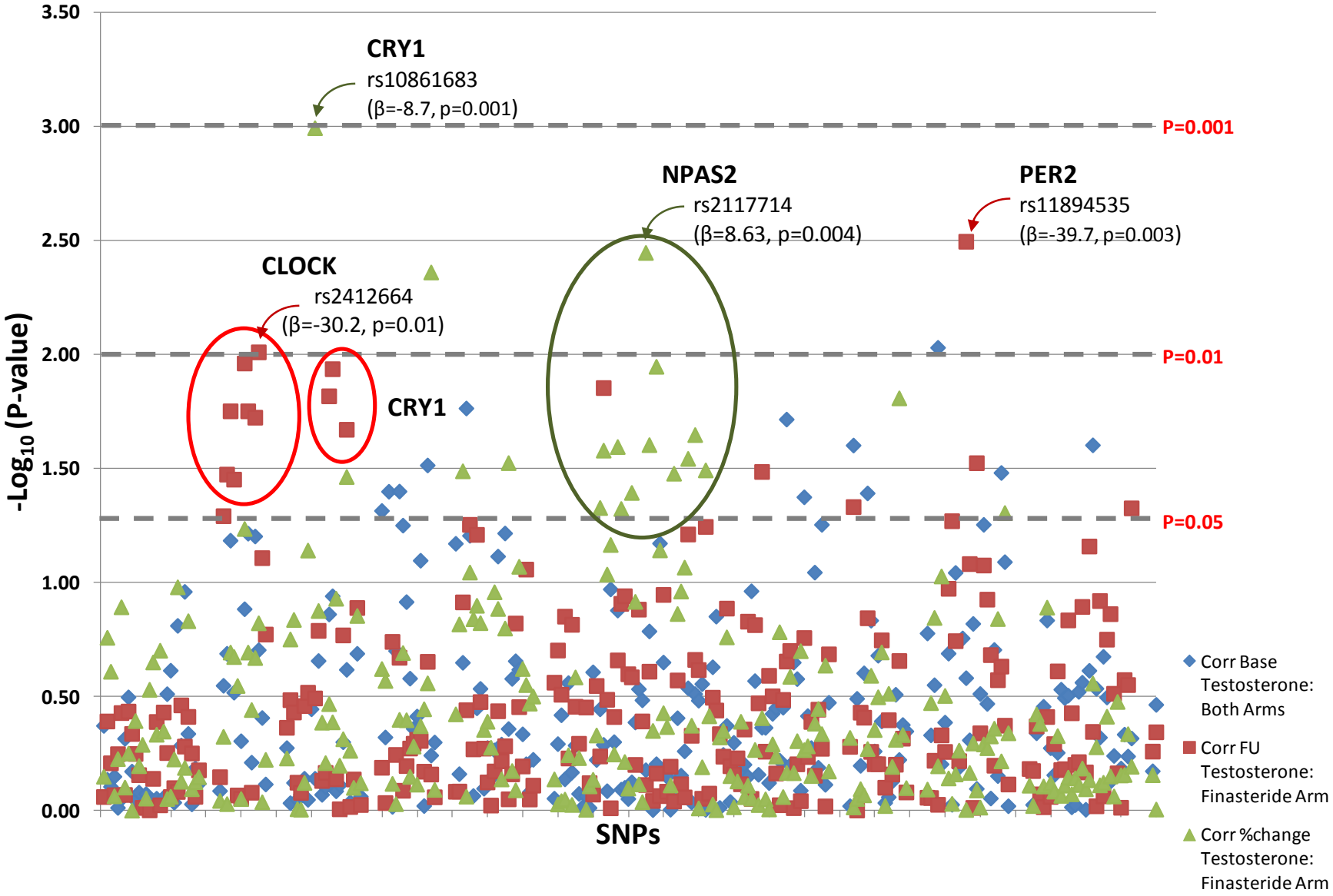

Figure 5. Correlation between individual circadian gene variants on serum 3α diol G levels in the finasteride-treated men

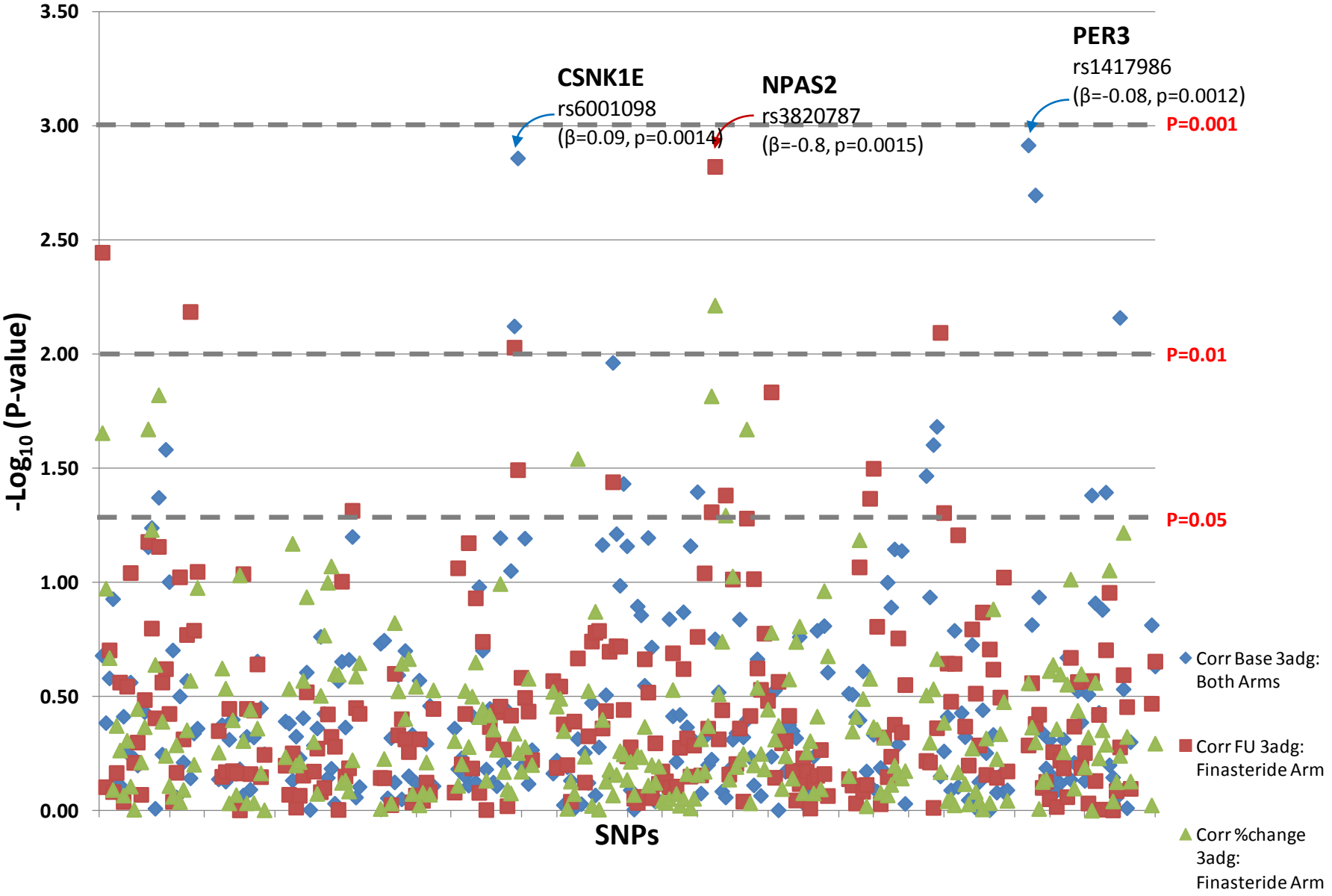

Figure 6. Correlation between individual circadian gene variants on serum sex hormone-binding globulin (SHBG) levels in the finasteride-treated men